Human Participant Protections Education for Research Teams

U.S. Department of Health and Human Services
National Institutes of Health

Last revised: November 2002.

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Preface

The mission of the National Institutes of Health (NIH) is to improve human health through biomedical and behavioral research. Conducting research involving human participants* is a necessary and important part of that mission.

The NIH is committed to the ethical conduct of research and to providing appropriate education for researchers whose work involves human participants. In October 2000, the NIH established a policy requiring education in the protection of human research participants for all investigators and key personnel submitting NIH applications for grants or proposals for contracts, or receiving new or non-competing awards.

As part of its commitment to the protection of human participants, the NIH has developed this tutorial: "Human Participant Protection: Education for Research Teams." This course offers one option to fulfill the obligation for education in the area of human participant protection.

* This tutorial uses the term human participant to mean human subject, the term used in the Federal regulations. Please see the Glossary for additional definitions of terms.

This course is intended for use by those involved in the design and conduct of biomedical and behavioral research involving human participants, including:

- Principal and Associate Investigators
- Nurse coordinators
- Data managers
- Statisticians

This tutorial presents common concepts, principles, and issues related to protection of human participants, including principles of bioethics and basic legal standards. This document includes narrative text and case studies to provide research teams with a multifaceted approach to human subjects protection.

The information presented is neither prescriptive nor exhaustive and is intended to act as a companion piece to your institutional policy in addition to local, state, and federal regulations applicable to human research. The tutorial will help you and your team identify research activities that involve human participants and help you understand how to protect the rights and welfare of all human participants involved in research.

Chapter 1: History

Before discussing the current system for the protection of human participants in research, it is important to review some of the significant historical events that have influenced current ethical guidelines and Federal regulations.

In this Chapter, the following topics will be discussed:

- **Historical Events**
- **The Development of Codes of Research Ethics**
- **Guiding Principles**
- **The Statutory Framework**
- **Federal Regulation and the "Common Rule"**
- **Food and Drug Administration Guidelines**

Learner Objectives

- Identify and describe at least five historical events that have influenced current ethical guidelines and Federal regulations
- Identify the three fundamental ethical principles that guide the ethical conduct of research involving human participants
- Describe the role of international guidelines in the protection of human participants

Historical Events

The Goals and Principles of Human Participant Protection

The principles of protection of human participants in research were established in the Belmont Report in 1979. The Belmont Report was prepared by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research at the request of the Secretary of the Department of Health and Human Services (DHHS). The report identified three principles essential to the ethical conduct of research with humans: respect for persons, beneficence, and justice. These three principles formed the foundation for the conduct of research, including guidelines for obtaining informed consent, respect for privacy and confidentiality, and risk/benefit assessment.

Research participants are essential to the conduct of research, enabling researchers to make progress and discoveries in the fields of medicine and health. As such, the relationship between researchers and participants is critical and should be based on accurate information, trust, and respect.

Nazi Medical War Crimes

Although not the first example of harmful research on unwilling human participants, the experiments conducted by Nazi physicians during World War II were unprecedented in their scope and the degree of harm and suffering to which human beings were subjected.

"Medical experiments" were performed on thousands of concentration camp prisoners and included deadly studies and tortures such as injecting people with gasoline and live viruses, immersing people in ice water, and forcing people to ingest poisons.

In December 1946, 23 physicians and administrators, many of them leading members of the German medical hierarchy, were indicted before the War Crimes Tribunal at Nuremberg for their willing participation in the systematic torture, mutilation, and killing of prisoners in experiments. Despite the arguments of the German physicians that the experiments were medically justified, the Nuremberg Military Tribunals condemned the experiments as "crimes against humanity"; 16 of the 23 physicians were found guilty and imprisoned, and 7 were sentenced to death. In the August 1947 verdict, the judges included a section called "Permissible Medical Experiments." This section became known as the *Nuremberg Code* and has formed the basis for ethics codes internationally.

The Tuskegee Syphilis Study

The most notorious example in the United States of prolonged and knowing violations of the rights of a vulnerable group of research participants was the long-term study of black males conducted at Tuskegee by the United States Public Health Service. This study was initiated in the 1930s as an examination of the natural history of untreated syphilis; it continued until 1972.

More than 400 black men with syphilis participated, and about 200 men without syphilis served as controls. The men were recruited without informed consent and, in fact, were misinformed that some of the procedures done in the interest of research (e.g., spinal taps) were actually "special free treatment."

By 1936, it was apparent that many more infected men than controls had developed complications, and 10 years later, a report of the study indicated that the death rate among those with syphilis was about twice as high as it was among the controls. In the 1940s, penicillin was found to be effective in the treatment of syphilis. The study continued, however, and the men were neither informed nor treated with the antibiotic.

The first accounts of this study appeared in the national press in 1972. The resulting public outrage led to the appointment of an ad hoc advisory panel by the Department of Health, Education and Welfare to review the study and advise on how to ensure that such experiments would never again be conducted. Among the recommendations was the request that Congress establish a "permanent body with the authority to regulate, at least, all federally supported research involving human subjects."

In acknowledgement of its responsibility, the Government continues to compensate surviving participants and the families of deceased participants.

The Jewish Chronic Disease Hospital Study

In 1963, studies were undertaken at New York's Jewish Chronic Disease Hospital to understand whether the body's inability to reject cancer cells was due to cancer or debilitation. Previous studies had indicated that healthy persons reject cancer cells promptly, and the researchers allegedly believed that the debilitated patients would also reject the cancers but at a substantially slower rate when compared to healthy participants.

These studies involved the injection of foreign, live cancer cells into patients who were hospitalized with various chronic debilitating diseases. Consent had been given orally, but did not include a discussion on the injection of cancer cells, and consent was not documented. The researchers felt that documentation was unnecessary because it was customary to undertake much more dangerous medical procedures without the use of consent forms.

Further, patients were not told that they would receive cancer cells, because the researchers felt it would unnecessarily frighten them. Researchers defended this view with the assertion that they had good cause to predict that the cancer cells were going to be rejected.

In subsequent review proceedings conducted by the Board of Regents of the State University of New York, it was found that the study had not been presented to the hospital's research committee and that the physicians responsible for the patients' care had not been consulted. The researchers were found guilty of fraud, deceit, and unprofessional conduct.

The Willowbrook Study

The vulnerability of children, especially institutionalized children, as participants in research is demonstrated in a series of studies conducted from 1963 through 1966 at the Willowbrook State School, a New York institution for "mentally defective" children. In order to gain an understanding of the natural history of infectious hepatitis under controlled circumstances, newly admitted children were deliberately infected with the hepatitis virus. Researchers defended the deliberate injection of these children by pointing out that the vast majority of them would acquire the infection anyway while at Willowbrook, given the crowded and unsanitary conditions, and because only children whose parents had given consent were included.

During the course of these studies, Willowbrook closed its doors to new patients, claiming overcrowded conditions. However, the hepatitis program, because it occupied its own space at the institution, was able to continue to admit new patients. Thus, in

some cases, parents found they were unable to admit their children to Willowbrook unless they agreed to their participation in the studies.

This controversial case raised important questions about the adequacy and freedom of consent, inadequate disclosure of the child's risk of later developing chronic liver disease, and the lack of information given to parents about access to doses of gamma globulin for their children.

Below is a timeline of these events and many others that shaped the current system of guidelines for protection of human participants.

1932–1972: Tuskegee Syphilis Study: This research used disadvantaged, rural black men to study the course of an untreated disease. The men were offered free examinations and medical care but were not informed of their disease, that they were participating in research, or that the research would not benefit them. Further, in order not to interrupt the project, participants were deprived of demonstrably effective treatment long after such treatment was discovered and had become generally available. (*Racism and Research: The Case of Tuskegee Syphilis Study*. Hastings Center Report, December 1978. p. 22-29).

1939–1945: Nazi Experiments During World War II: Prisoners in Nazi concentration camps were forced to undergo experiments that included exposing them to extreme temperatures, mutilating surgery, and lethal pathogens. The gruesome experiments that maimed and killed helpless prisoners outraged the world and resulted in criminal indictments against senior Nazi doctors, as well as calls for international regulation of medical experiments.

1944–1974: Human Radiation Experiments: The U.S. Government sponsored several thousand human radiation experiments. In the majority of cases, the experiments were conducted to advance biomedical science. Some experiments were conducted to advance national interests in defense or space exploration, and some served both biomedical and defense or space exploration purposes. Most of these studies involved radioactive tracers administered in amounts not likely to cause physical harm. However, during this period, little attention was given to issues of fairness in the selection of participants. Further, research was conducted on participants without their awareness or consent and on participants not likely to derive direct medical benefit.

1946: Nuremberg Doctors' Trial: The individuals who conducted Nazi experiments during WWII were tried separately from other war criminals because of their professional status as physicians and the horrendous and unique nature of their crimes. They were found guilty of murder, torture, and other atrocities.

1947: Nuremberg Code: During the trial at Nuremberg, the judges codified fundamental ethical principles for the conduct of research. The Nuremberg Code set forth ten conditions to be met before research could be deemed ethically permissible. The

Nuremberg Code became the first international standard for the conduct of research and introduced the modern era of protection for human research participants.

1948: The Universal Declaration of Human Rights was adopted by the United Nations. The Universal Declaration asserted the principle that each human being was entitled to certain rights and freedoms. The Declaration was inspired by atrocities committed during World War II and the conviction that human rights needed to be preserved at the international level.

1953: The Clinical Center of the NIH produced the first U.S. Federal policy for the protection of human participants. This policy provided a mechanism for prospective review of research by individuals who had no direct involvement or intellectual investment in the research. This system served as the precedent for the IRB system.

1963: Jewish Chronic Disease Hospital Study: Studies were undertaken at the Jewish Chronic Disease Hospital to develop information about the human transplant rejection process. Live cancer cells were injected into chronically ill and debilitated patients who had been told they were receiving a skin test. The patients were given information about the test, but consent was not documented or signed. The researchers were eventually prosecuted and found guilty of fraud, deceit, and unprofessional conduct.

1963: The Willowbrook Study: From 1963 to 1966, studies were carried out at Willowbrook State School, a New York institution for "mentally defective persons." These studies were designed to gain an understanding of the natural history of infectious hepatitis and, subsequently, to test the effects of gamma globulin in preventing or ameliorating the disease. The participants, all children, were deliberately infected with the hepatitis virus. Early participants were fed the stools of infected persons. Later, subjects received injections of more-purified virus preparations. Researchers defended the deliberate injection of these children by noting that the majority would acquire the disease anyway while at Willowbrook, adding that perhaps it would be better for them to be infected under controlled research conditions. During the course of these studies, Willowbrook closed its doors to new inmates, claiming overcrowded conditions. However, the hepatitis program was able to continue to admit new patients because it occupied its own space at the institution. Thus, in some cases, parents found they were unable to admit their children to Willowbrook unless they agreed to their participation in the studies.

1964: Declaration of Helsinki: A landmark international agreement adopted by the World Medical Association recommending ethical standards in medical research. A fifth revision of the document, approved in October 2000, addresses issues raised as a result of rapid expansion of biomedical research and international research activities. The revised Declaration of Helsinki can be found on the WMA Web site, http://www.wma.net/.

1972: Exposé of Tuskegee Study: The discovery of the involvement of the U.S. Public Health Service in violating the rights of research subjects in the Tuskegee Study caused outrage among the public and the study participants. Despite the Government's attempts

to make amends to study victims and their families, reverberations from the study and public mistrust in research continue.

1974: Federal legal protection for human research participants begins. After the Tuskegee Syphilis Study was exposed, the Senate Committee on Labor and Human Resources held hearings on this study and other alleged health care abuses. The outcomes of these hearings were: 1) the enactment of the National Research Act of 1974 requiring the Department of Health, Education, and Welfare to codify its policy for the protection of human subjects into Federal regulations; and 2) the formation of the National Commission for the Protections of Human Subjects of Biomedical and Behavioral Research, which would draft the Belmont Report.

1979: Belmont Report: The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research wrote the report entitled *Ethical Principles and Guidelines for the Protection of Human Subjects of Research.* This is the cornerstone document of ethical principles and Federal regulations for the protection of research participants based on respect for persons, beneficence, and justice.

1980: The Food and Drug Administration establishes regulations for clinical research. These can be found in the *Code of Federal Regulations*, Title 21, Part 50.

1982: CIOMS Guidelines: The Council for the International Organization of Medical Sciences (CIOMS) published the *International Ethics Guidelines for Biomedical Research Involving Human Subjects* (CIOMS *Guidelines*). These are designed to guide researchers from more technologically advanced countries in conducting research in developing countries.

1991: The Common Rule. The Federal Policy for the Protection of Human Subjects was adopted in 1991, covering research supported by the Departments of Agriculture, Energy, Commerce, HUD, Justice, Defense, Education, Veterans Affairs, Transportation, and HHS, as well as the NSF, NASA, EPA, AID, Social Security Administration, CIA, and the Consumer Product Safety Commission. The provisions are identical to DHHS Regulations (45 CFR 46, Subpart A).

1993: Human radiation experiments are revealed.

1994: President Clinton creates the Advisory Committee on Human Radiation Experiments to investigate human radiation experiments during the period 1944 to 1974; examine cases in which radiation was intentionally released into the environment for research purposes; identify ethical and scientific standards for evaluating these events; and make recommendations to ensure that past wrongdoings will not be repeated.

1995: The National Bioethics Advisory Commission (NBAC) is established to promote the protection of the rights and welfare of human participants in research, identify bioethical issues arising from research on human biology and behavior, and make

recommendations to governmental entities regarding their application. The NBAC ended its term in 2001.

2000: Increased Focus on Protection of Human Research Participation. The Office of Human Research Protections (OHRP) was established within the U.S. Department of Health and Human Services. This both elevated and replaced the NIH Office for Protection From Research Risks (OPRR). The OHRP provides leadership for all 17 Federal agencies that carry out research involving humans under the Common Rule regulations. The Office focuses entirely on protection of human participants in research and supervision of Institutional Review Boards.

The Development of Codes of Research Ethics

The Nuremberg Code

The Nuremberg Code served as the first set of principles outlining professional ethics for medical researchers. The ten points included the statement that "voluntary consent of the human subject is absolutely essential." The Code also established that animal experimentation should precede human experimentation; all unnecessary physical and mental suffering and injury should be avoided; the degree of risk to participants should never exceed the "humanitarian importance of the problem" and should be minimized through "proper preparations"; and that participants should always be at liberty to withdraw from experiments. This set of points established the basic principles that must be observed in order to satisfy moral, ethical, and legal concepts in the conduct of human participant research. The Code has been the model for many professional and governmental codes since the 1950s and has, in effect, served as the first international standard for the conduct of research.

Declaration of Helsinki

The Declaration of Helsinki was developed by the World Medical Association for use by the medical community following dissemination of the Nuremberg Code. The Declaration considers the conduct of clinical research and makes an important distinction between therapeutic and nontherapeutic research. However, this distinction was eliminated in later versions of the Declaration. Like the Nuremberg Code, the Declaration made informed consent a central requirement for ethical research while allowing for surrogate consent when the research participant is incompetent, physically or mentally incapable of giving consent, or a minor. The Declaration also states that research with these groups should be conducted only when the research is necessary to promote the health of the population represented and when this research cannot be performed on legally competent persons. It further states that when the subject is legally incompetent but able to give assent to decisions about participation in research, assent must be obtained in addition to the consent of the legally authorized representative. Further information about the Declaration of Helsinki, in addition to translations of the Declaration into languages other than English, can be found at: http://www.wma.net/

The Declaration has been revised five times, most recently in October 2000, and includes in its 32 principles the statement that "the benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods." Although it says that this does not exclude the use of placebo or no treatment, in studies where no proven prophylactic, diagnostic, or therapeutic method exists, this stipulation is very controversial, since some interpret it to mean that a placebo should never be used when effective therapy is available, regardless of the seriousness of the condition being studied.

The Declaration is important in the history of research ethics as the first significant effort of the medical community to regulate itself.

CIOMS Guidelines

The Council for International Organizations of Medical Sciences (CIOMS) is an international, nongovernmental, not-for-profit organization established jointly by WHO and UNESCO in 1949.

CIOMS serves the scientific interests of the international biomedical community in general and has been active in promulgating guidelines for the ethical conduct of research, among other activities. CIOMS promulgated guidelines in 1993 entitled *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. These 15 guidelines address issues including informed consent, standards for external review, recruitment of participants, and more. The Guidelines are general instructions and principles of ethical biomedical research. CIOMS is in the process of revising the *Guidelines* to address emerging issues in genetic research, commercial research, and research in developing countries. For further information about CIOMS and the *Guidelines*, refer to http://www.cioms.ch/

Belmont Report

In the 1950s and 1960s, Federal funding for biomedical research increased dramatically. Along with increased interest and funding, there was heightened public concern about research abuses such as the Tuskegee Study and other reported biomedical abuses.

In response to this public outcry, in 1974, Congress established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research to make recommendations for the conduct of research involving humans. The primary task of the National Commission was to identify the ethical principles that would guide all research involving humans. In 1979, the National Commission wrote the Belmont Report, *Ethical Principles and Guidelines for the Protection of Human Subjects,* which serves as the cornerstone of ethical principles upon which Federal regulations for the protection of human research participants are based. The Belmont Report can be found at the following site: http://ohrp.osophs.dhhs.gov/humansubjects/guidance/belmont.htm

Guiding Principles

In 1979, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research wrote the report entitled *Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, commonly called the "Belmont Report." In this report, the Commission identified and described the basic ethical principles that underlie research. The Commission considered the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine in order to "know what activities ought to undergo review for the protection of human subjects of research." The report also describes the assessment of risk/benefit criteria in the determination of appropriateness of research on participants, appropriate guidelines for this assessment, and the nature and definition of informed consent. The three fundamental ethical principles that guide the ethical conduct of research involving human participants are:

1. **Respect for Persons (autonomy)**
2. **Beneficence**
3. **Justice**

Respect for Persons

The principle of respect for persons incorporates at least two ethical standards:

1. Individuals should be treated as autonomous agents.

"An autonomous person is an individual capable of deliberation about personal goals and of acting under such deliberation. To respect autonomy is to give weight to the autonomous person's considered opinions and choices while refraining from obstructing his or her actions …." (Belmont Report).

Prospective research participants must be given the information they need to determine whether or not to participate in a study. There should be no pressure to participate and ample time to decide. Respect for persons demands that participants enter into the research voluntarily and with adequate information. This is called *informed consent*.

2. Persons with diminished autonomy may need additional protections.

Special provision may need to be made when comprehension is severely limited or when a class of participants is considered incapable of informed decision making (such as with children or people with severe developmental disorders or dementias). Even for these persons, however, respect requires giving them the opportunity to choose, to the extent they are able, whether or not to participate in research activities. In some cases, respect for persons may require seeking the permission of other parties, such as a parent or legal guardian. The

judgment that someone lacks autonomy should be periodically reevaluated and may vary in different situations.

Beneficence

Human participants are treated in an ethical manner not only by respecting their decision and protecting them from harm, but also by making efforts to secure their well-being.

The principle of *beneficence* obligates the researcher to maximize possible benefits and minimize possible harm.

The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite inherent harms or risks. Balancing risks and benefits is an important consideration. The goal of much research is societal benefit; however, in the interest of securing societal benefits; no individual shall be intentionally injured.

Justice

The ethical considerations of risks versus benefits leads to the question of *justice*. This principle requires that participants be treated fairly and involves questions such as: Who should bear the risks of research, and who should receive its benefits?

Justice is a difficult and complex ethical issue. Attempts must be made at all times in a study to distribute the risks and benefits fairly and without bias. Also, unless there is clear justification, research should not involve persons from groups that are unlikely to benefit from subsequent applications of the research. The concept of justice may be questioned when deciding who will be given an opportunity to participate, who will be excluded, and the reasons for exclusion. When making such decisions, the researcher must ask: Are some classes of persons being selected simply because of their availability, their compromised position, or their vulnerability—rather than for reasons directly related to the problem being studied?

The Statutory Framework

In addition to ethical considerations, the Federal Government mandates certain legal standards for protection of humans in research. These standards are set forth in the *Code of Federal Regulations*, Title 45 CFR Part 46 (see http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm). Subpart A, the basic policy for protection of human research subjects, is referred to as the "Common Rule." The regulations were enacted in 1991 and apply to all federally funded human research. Once a research activity is deemed human subject research, the Department of Health and Human Services requires review by Institutional Review Boards and imposition of certain standards for informed consent.

Other standards apply for research submitted to the Food and Drug Administration for review and approval. (See http://www.fda.gov/ and http://www.fda.gov/oc/gcp/guidance.html for information regarding good clinical practice for research studies involving human participants in FDA-regulated products.)

Federal Regulation and the "Common Rule"

By 1981, the Department of Health and Human Services and the Food and Drug Administration published regulations based on the Belmont principles, establishing rules for research involving human subjects. In 1991, 17 Federal departments and agencies agreed to harmonize their policies on protection of human participants in research and adopt a single standard. This standard policy for federally funded research is set forth in Title 45, *Code of Federal Regulations*, Part 46.

This policy covers research funded by the Departments of Agriculture, Energy, Commerce, HUD, Justice, Defense, Education, Veterans Affairs, Transportation, and Health and Human Services (DHHS), as well as the National Science Foundation (NSF), NASA, Environmental Protection Agency (EPA), Agency for International Development (AID), Social Security Administration, Central Intelligence Agency (CIA), and Consumer Product Safety Commission.

Subpart A of the Regulation is the DHHS Policy for the Protection of Human Research Subjects. This DHHS policy is referred to as the "Common Rule."

Subpart B of the Regulations addresses additional protections extended to research involving fetuses, pregnant women, and human *in vitro* fertilization. Subpart C pertains to protection of prisoners who are participants in human subject research. Subpart D addressed protections for children who participate in research. The regulations can be found at: http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm

Food and Drug Administration Guidelines

The FDA regulates research involving products regulated by the FDA, including research and marketing permits for drugs, biological products, and medical devices for human use, etc. whether or not Federal funds are used.

The FDA guidelines for informed consent and protection of human subjects are found at: http://www.access.gpo.gov/nara/cfr/waisidx_00/21cfr50_00.html

Chapter 2: The Basics

This chapter defines the basic terms used in the Federal guidelines and regulations protecting participants in research. Understanding who is the research participant and when a research study includes human participants guides the researcher and team in applying the appropriate policies. The roles and responsibilities of the researcher and the team in relation to human participant protections are explored.

In this Chapter, the following topics will be discussed:

- **Who, When, Why?**
- **Participant Selection**
- **Vulnerable Population**
- **Special Issues in Participant Selection and Recruitment**
- **Protection of Privacy and Confidentiality**
- **Case Study**

Learner Objectives

- Recognize when a study requires human participant protections
- Describe the responsibilities of at least four organizations or individuals in protecting human participants
- Identify issues to consider when selecting participants for a study and the policies and regulations that apply to special groups
- Define privacy and confidentiality as it applies to protecting human participants and describe how these can be maintained throughout the research process

Who, When, Why?

Research is a systematic investigation (including development, testing, and evaluation) designed to discover or contribute to a body of generalizable knowledge. Not all research involves human participants, but when they are involved, researchers and their teams are legally and ethically obligated to protect them.

WHO is the research participant?

The human participant is a living individual about whom a researcher obtains either: (1) data through intervention or interaction with the individual; or (2) identifiable private information.

Can other individuals be research participants?

In the course of participating in a research study, a participant may provide information to investigators about other persons, such as a spouse, relative, friend, or social acquaintance. The information may be sensitive (e.g., regarding alcohol or drug use, diet, or lifestyle) and personal. These other persons are referred to as "third parties." Questions have arisen regarding third parties and whether they should be considered human subjects.

If information is obtained about a third party from a research participant, then these third parties may be considered human subjects under certain circumstances. However, if no private and individually identifiable information is obtained about third parties, then NIH generally does not consider them human subjects.

Nevertheless, investigators should treat all research information about individuals as confidential. Identifying information, whether about a human subject or a third party, should be kept secure and protected from inappropriate disclosure.

WHEN does research require the inclusion of human participant protections?

Protection of participants covers a wide range of research, including that which involves tissue specimens, medical records, genetic material, behavioral and/or biomedical assessments, and treatments. In addition to the traditional understanding of research participation, legal obligations to protect human participants apply to research that uses:

- Bodily materials, such as cells, blood or urine, tissues, organs, and hair or nail clippings, even if the researcher did not collect these materials.
- Residual diagnostic specimens, including specimens obtained for routine patient care that would have been discarded if not used for research.
- Private information, such as medical data, that can be readily identified with individuals, even if the information was not specifically collected for the study in question. Research on cell lines or DNA samples that can be associated with individuals falls into this category.

Each researcher must decide if the study includes human participants and, if so, become familiar with the regulations governing the rights and safety of research participants.

The decision is governed by:

- The researcher's institutional rules.
- The requirements of the researcher's institutional review board (IRB).
- Regulations in the *Code of Federal Regulations*, Title 45, Part 46: Protection of Human Subjects, and Food and Drug Administration *Regulations* 21CFR, Part 50, 56.

To help make this important decision, researchers may want to review the Human Subjects Regulations Decision Charts and Research on Human Specimens.

Exempt Research

Some research that involves human participants may be exempt from the requirements of the Common Rule and from IRB review. This should not be determined by the investigator alone. It is desirable to obtain this determination from a party not directly involved in the research, such as a department head, in accordance with institutional policies and in consultation with the institution's IRB. The exemption categories found in 45 CFR 46.101(b) are listed in the Chapter entitled "IRB Review." For more information, see Chapter 4, "IRB Review."

WHY is it important to protect human research participants?

Conducting research involving humans is a necessary and crucial step in improving human health through biomedical and behavioral research. In this era of rapidly advancing medical technology, increasing complexity and pace of research, revolutionary genetic research, and ever-increasing threats to personal privacy, the protection of human participants is a priority. Researchers and the research team have a fundamental responsibility to safeguard the rights and welfare of the people participating in their research activities.

Emphasis on enhancing protection is needed to:

- Promote the safety and well-being of human participants in research.
- Maintain the ethical values and principles underlying research.
- Implement scientifically valid research.
- Allay concerns by the general public about the responsible conduct of research.

The responsibility to protect participants volunteering in research belongs to a variety of individuals, groups, and organizations:

- Federal agencies, such as the National Institutes of Health (NIH) and the Food and Drug Administration (FDA), and Office of Human Research Protections (OHRP) which provide policies and guidelines concerning participant protections for clinical trials research
- Funding agencies/sponsors, which are responsible for ensuring that grantees adhere to the Federal regulations
- Scientific peer-review groups, institutional review boards, and data and safety monitoring boards, which review research and oversee human participant protections at different stages in the research process

The researcher conducting the study has the primary responsibility to ensure that participants in research are fully informed of their rights and properly protected.

The researcher is specifically responsible for ensuring that:

- The study is properly designed, scientifically sound, and yields valid results.
- Participants meet selection and eligibility requirements.
- The study is approved by the IRB and conducted according to the protocol.
- Informed consent is appropriately obtained.
- Protocol changes and adverse events are reported to the appropriate boards and authorities.
- The rights and welfare of participants are monitored throughout the trial.
- All members of the research team are qualified and trained in research methods and human participant protections.

Research team members (key personnel) whose responsibilities are delegated by the researcher also have a role in ensuring integrity of the study by consistently applying procedures and ensuring that the rights of participants are safeguarded.

Research team members are typically responsible for:

- Day-to-day protocol decision making related to study conduct.
- Participant recruitment, selection, and eligibility.
- Clarification of the complexities of the protocol to the participant and others.
- Collection of participant information and entry of data using procedures to maintain privacy and confidentiality.
- Ensuring that the rights and welfare of participants are monitored throughout the study.

Participant Selection

In selecting participants for research, researchers are responsible for ensuring that selection is equitable. No individual or group should be overburdened without the acquisition of potential benefits. This is based on the principle of *justice*. The researcher must consider:

- The population from which the sample is drawn.
- The feasibility of acquiring the number of participants needed.
- Recruitment procedures that ensure an equitable distribution across the population.

Inclusion and exclusion criteria are developed in the planning and written into the protocol. These should take into account the 1994 NIH *Guidelines on the Inclusion of Women and Minorities in Research* and any vulnerable populations. The most recent version of this policy is found at http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm

The *Guidelines* issued by NIH for the inclusion of women and minorities as participants in research require the inclusion of women and minority populations "so that the research findings can be of benefit to all persons at risk of the disease, disorder, or condition under study." If a proposed study includes a population in which women and minorities are not appropriately represented, the researcher must provide "a clear and compelling rationale" for their exclusion or inadequate representation.

The researcher must consider other issues with the potential to affect selection of participants. Patients may also be susceptible to real or imaginary pressure to participate. If a researcher also serves as a patient's primary physician, the patient may feel obliged to participate in the research out of a desire to please or out of fear that failure to do so will result in hostility or abandonment. Patients who are dependent upon a particular facility for their care (e.g., Veterans Administration hospitals, Indian Health Service hospitals, or community health clinics) may feel that they will be treated less well or with less favor if they refuse to participate in research.

Vulnerable Populations

Vulnerable research participants are persons who are relatively or absolutely incapable of protecting their own interests. The researcher and research team should be cognizant of the special problems of research involving vulnerable populations, justify the proposed involvement of these populations in the research, and include additional safeguards for their safety and welfare. These populations include:

- Children.
- Individuals with questionable capacity to consent.
- Prisoners.
- Fetuses and pregnant women.
- The terminally ill.
- Students/employees.
- Comatose patients.

Brief information about the regulations on research with children, individuals with questionable capacity to consent, and prisoners are presented, but the researcher and team should be familiar with all of the policies by visiting websites suggested in this section and in Appendix C: Resources.

Research with Children

Research involving children demands a particularly high level of care and consideration by investigators. In recent years, ethical and legal standards have changed, and investigators who conduct research in this area should consult with their IRBs.

The issue of children as research subjects is a complex one since they are not considered able to make informed choices independently. Further, exposure of children, particularly healthy children, to more than minimal risks must be weighed carefully.

When including children in research, the role of the family should be considered in devising the protocol as well as in obtaining informed consent from the parents or guardians. If the research is based in schools, appropriate involvement and permission must be obtained from the school. Adequate measures must be developed to protect children's privacy and to ensure that their participation does not stigmatize them in the present or future.

The regulation pertaining to children as research participants is found in 45 CFR 46, Subpart D.

Risk/benefit categories found in this regulation include those:

- Not involving greater than minimal risk.
- Involving greater than minimal risk but presenting the prospect of direct benefit to the child.
- Involving greater than minimal risk and no prospect of direct benefit to the child, but likely to yield knowledge about the child's disease.
- Not otherwise approvable, but presenting an opportunity to understand, prevent, or alleviate a serious problem for children.

In 1998, the NIH wrote a policy and *Guidelines on the Inclusion of Children as Research Participants* in all studies supported and/or conducted by the NIH. The goal of this policy is to increase the participation of children in research so that adequate data will be developed to support the treatment modalities for disorders and conditions affecting adults that may also affect children. Proposals for research involving human participants must include a description of plans for including children or an explanation for their exclusion. This policy is found at http://grants.nih.gov/grants/guide/notice-files/not98-024.html. The FDA has published an Interim Rule entitled "Additional Safeguards for Children in Clinical Investigations of FDA-regulated products" (21 CFR Parts 50 and 56). This rule can be found at the following address: http://www.fda.gov/ohrms/dockets/98fr/042401a.htm

Research With the Decisionally Impaired

Research involving individuals with questionable capacity to consent requires careful consideration in order to provide these participants with additional safeguards. This

vulnerable population may include persons with psychiatric illnesses, neurologic conditions, substance use history, and various metabolic disorders. Some individuals may not be able to give informed consent, so "permission" for certain kinds of research can be given by a legally authorized representative and "assent" of the participant is substituted.

Research with Prisoners

Prisoners are confined under the strict control of people whom they must please and to whom they must appear cooperative if they are to earn their release. These potential participants may believe, probably as a result of their dependent situation, that their agreement to participate in research will be viewed positively by their wardens. In addition, such individuals are readily available in large numbers. In the past, prisoners have accepted the risks of research in disproportionate numbers, while the benefits of the research in which they participated went to all segments of the population. Therefore, special regulations are in place that restrict the involvement of prisoners in research. For example, it is appropriate to include a prisoner as a voting member of the IRB when decisions are made for studies that involve prisoners.

With these caveats and an understanding of the Federal regulations in mind, researchers must also be careful not to overprotect vulnerable populations to the extent that they are excluded from participating in research in which they wish to participate, particularly where the research involves therapies for conditions with no available treatments. So, too, patients with serious or poorly understood disorders may want to participate repeatedly in research designed to provide a better understanding of their conditions. The fact that participants may be either patients of the principal researcher or patients in the clinic or hospital in which the researcher conducts the study should not preclude them from the opportunity to choose to participate as often as they wish.

Special Issues in Participant Selection and Recruitment

Stigmatization as a Result of Participation in Research

One issue to be considered by investigators is whether participants will suffer stigmatization as a result of their participation in research. When research is conducted on behaviors, lifestyles, or conduct that is unpopular or even illegal, the mere act of being included in a study may cause an individual to be labeled in a negative manner. If an individual is identified as a potential participant, the person who attempts to recruit that individual must be sensitive to this issue.

The informed consent form must indicate the researcher's obligation to report certain observations, if such duty exists, as well as to offer assistance to participants in need.

Note that in circumstances where there is a particularly high risk of stigmatization based on participation in a research project, and where the only record of the identity of

individual participants is found in the signed informed consent document, the IRB may waive the requirement that written informed consent be obtained [45CFR46.117(c)].

Another decision is whether to reveal participation in the research in the individual's medical record. As always, care must be taken to keep research data confidential.

Payment of Research Participants

Several other issues may affect the voluntary nature of participation in research. One such dilemma is whether to pay research participants. The investigators or research sponsors sometimes pay participants; the payment may be for time, effort, or discomfort associated with participation. There are no clear rules or standards for payment other than a general prohibition against coercion or the exercise of undue influence. There is no agreement about whether it is right to pay research subjects. Further, there are no clear rules about when to pay research subjects or how much is appropriate, so each research organization must create and document its own rules.

Financial Conflicts of Interest

Another issue currently the subject of much debate is what constitutes a financial conflict of interest on the part of an investigator or institution. In 1995, a regulation was promulgated to promote objectivity in research (42 CFR 50.601); it requires institutions to have a policy and procedures in place to manage, reduce, or eliminate investigators' conflict of interest. Concerns about this issue have affected research and led to calls for more thorough disclosure of ties between the research community and industry. Research that leads to commercially viable products and services has also led to renewed scrutiny in this area.

Protection of Privacy and Confidentiality

Privacy is defined in terms of having control over the extent, timing, and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others. When participants in research give information about themselves to the research team or institution, they do so in a relationship of trust. They expect that information to be shared only as necessary. The research team must respect the participant's trust and not betray the confidence placed in them. *Privacy* has also been defined as freedom from unwanted intrusion. Thus, in the field of medicine and health, privacy may mean the right not to know certain information, even about oneself, and the right to prevent others from obtaining or using personal information.

Rapid advances in the acquisition, storage, analysis, and communication of data by electronic means, combined with the recent advances in biomedical research, have posed challenges for the clinical research community. One of these challenges is in the maintenance of confidentiality of personally identifiable health information. The goal of the research community—and of society generally—should be to continue to protect the

confidentiality of research information without compromising the critical research necessary to improve human health.

Confidentiality

Physicians have always been bound to protect the information revealed by patients or discovered by physicians during the course of medical treatment. This is an ethical as well as a professional obligation. In the last several years, many states have also mandated a legal duty for hospitals, health insurers, physicians, and others who handle personal health information to protect this information from disclosure.

State laws on medical privacy vary widely in terms of scope and in the type of consent they require if information is to be released. In addition to state legislation protecting the collection, storage, and release of protected health information, some states have passed legislation regulating the use of medical information and, specifically, compelling nondiscrimination in the provision of health insurance, life insurance, and employment based on the receipt of medical (often genetic) information.

The first Federal statute on health privacy was enacted recently and is due to be implemented in April 2003. The Administrative Simplification provisions of the Health Insurance Portability and Accountability Act (HIPAA) of 1996 comprise three major parts: protection of individually identifiable health information (the "Privacy Rule"), security, and electronic transactions. The Privacy Rule regulates access to and disclosure of protected health information by certain entities.

Breaches of confidentiality are usually defined as disclosures to third parties, without patient consent or court order, of private information a physician has learned within the patient-physician relationship. Disclosure can be oral or written, by telephone or fax, or electronic—for example, via e-mail or health information networks.

Note that the right to privacy and/or confidentiality is not absolute under the law. Circumstances exist in which the duty to maintain confidentiality is considered less important than the duty to protect others. For example, in the case where a physician obtains information that an individual is a threat to others, there may be a legal duty to inform the police. Many states have statutes demanding the reporting of child abuse or the presence of infectious diseases. In the research setting, every effort is made by researchers to preserve privacy.

Confidentiality pertains to the treatment of information an individual has disclosed in a relationship of trust and with the expectation that it will not, without permission, be divulged to others in ways that are inconsistent with the understanding of the original disclosure. Researchers ordinarily use information participants have disclosed or provided voluntarily (i.e., with their informed consent) for research purposes. Under these circumstances, there is little reason for concern about privacy other than to ensure that appropriate confidentiality of research data is maintained. In most research, ensuring confidentiality can occur by following routine practices:

- Substituting codes for identifiers or encrypting identifiable data
- Removing face sheets (containing identifiers such as names and addresses) from survey instruments containing data
- Properly disposing of computer sheets and other papers
- Limiting access to identifiable data
- Educating the research staff on the importance of confidentiality
- Storing paper records in locked cabinets or assigning security codes to computerized records

In studies of participants with sensitive or stigmatizing information, including illegal or unpopular behavior (e.g., persons who have sexually abused children, tested positive for HIV, or sought treatment in a drug abuse program) or genetic information, keeping participants' identities confidential may be as important as, or more important than, protecting the data obtained about the participants. In such cases, any written record linking participants to the study can constitute a threat to confidentiality. Having participants in these studies sign consent forms may increase the risk of a breach of confidentiality because the consent form itself constitutes a record, complete with signature, which identifies particular individuals. Federal policy allows the IRB to waive the requirement for the researcher to obtain a signed consent form in cases in which it will be the only record linking participants to the research and in which a breach of confidentiality represents the principal risk of harm that might result from the research [45 CFR 46.117(1)].

When data are being collected about sensitive issues (e.g., illegal behavior, alcohol or drug use, sexual practices or preferences), protection of confidentiality involves more than preventing accidental disclosures. There have been instances in which the identities of or research data about particular participants have been sought by law enforcement agencies, sometimes under subpoena and with the threat of incarceration of the uncooperative researcher. Under Federal law, and some state laws, researchers can obtain an advance Certificate of Confidentiality that will provide protection even against a subpoena for research data.

Certificates of Confidentiality

Certificates of Confidentiality are used by investigators to protect the identities of research participants, particularly in studies involving matters of a sensitive or stigmatizing nature. The statutory authority for Certificates is provided by the Public Health Service Act §301(d), 42 U.S.C. §241(d). The Public Health Service Act permits the Secretary of Health and Human Services to authorize persons engaged in biomedical, behavioral, clinical, or other research (including research on mental health and on the use and effect of alcohol and other psychoactive drugs) to protect the privacy of individuals who are the subjects of such research. When a Certificate is issued, researchers may not be compelled in any Federal, state, or local civil, criminal, administrative, legislative, or other proceedings to identify such research participants.

Case Studies

Chapter 2 – Case Study 1

Investigator X is a psychologist at a university in a large city. She wishes to conduct an epidemiological study of the prevalence of mental disorders in the city and has chosen to evaluate a representative sample from the community.

Prospective participants are called by research staff, informed about the study, and asked if they are interested in volunteering. Those who agree sign informed consent documents and are visited by a pair of research staff who describe the survey, which includes interviews and written questionnaires regarding participants' mental and emotional health.

While answering one of the survey questions about family life, a participant becomes upset and tells the research staff that he wants to withdraw from the study.

Q. What should the research team consider when deciding how to proceed?

A. The team should consider the following actions:

- The interview should be discontinued, and the participant assured that he does not have to continue.
- The research team may ask if there is someone they can call to help, and if the participant agrees, the team may contact that person.
- The research team should contact the research supervisor to inform them of what occurred.

Q. What should the research team *not* do?

A. The research team should not do either of the following:

- Compel or even encourage the participant to finish the interview
- Contact the participant's family without permission

Chapter 2 – Case Study 2

A study is looking at depressed adults ages 18 to 50. The study involves obtaining information about suicidal tendencies, based on assessments derived from written questionnaires and interviews. The Investigator has obtained a Certificate of Confidentiality.

Q. What information about participants must be kept confidential?

A. All individually identifiable private information must be kept confidential. The investigators have an obligation to describe in detail what information will be kept confidential and what steps they will take to maintain confidentiality.

In addition, the investigators should describe in the informed consent what information may not be disclosed to others. Participants should be informed that information that is disclosed voluntarily is not protected. Also, certain information must be disclosed to third parties by law:

- Information indicating a risk of harm to others (usually homicidal thoughts)
- Information indicating a risk of harm to self (usually suicidal thoughts)
- Disclosures about child abuse
- Disclosures about infectious diseases required to be reported to public health authorities

Chapter 3: Informed Consent

This chapter defines the basic terms used in the Federal guidelines and regulations protecting participants in research. Understanding who is the research participant and when a research study includes human participants guides the researcher and team in applying the appropriate policies. The roles and responsibilities of the researcher and the team in relation to human participant protections are explored.

In this Chapter, the following topics will be discussed:

- **Background**
- **Preparing the Consent Document for IRB Review**
- **Approaching Research Participants**
- **Special Issues in Informed Consent**
- **Case Study**

Learner Objectives

- Define informed consent and describe the elements that should be included in an informed consent document
- Describe conditions that may affect a person's capacity to consent and the responsibilities of the researcher in seeking consent from research participants
- Identify at least one new and emerging issue in informed consent that should be considered

Background

Once the researcher has a carefully defined research question, a valid design, and protocol for a research project, it is time to plan for the informed consent for those invited to participate. Planning involves deciding:

- What information is important to provide potential participants, both in writing and in discussions
- Who will present the information
- When, or at what point in the interactions with participants to provide the information
- How to assess the participant's understanding
- Who will obtain the participant's signature or agreement

This plan must be reviewed and approved by an IRB before approaching potential participants.

Informed consent, as a legal, regulatory, and ethical concept, has become widely accepted as an integral part of research. Current requirements for informed consent owe much to the legal system, but the underlying values are deeply embedded in American culture and the American character. Fundamentally, informed consent is based on respect for the individual, and, in particular, the individual's autonomy or capacity and right to define his or her own goals and make choices designed to achieve those goals in life. This right is well established in American jurisprudence and medical practice and applies to all types of medical interventions and clinical research.

Informed consent in research means more than simply obtaining the signature of the potential research participant. It is a process that involves conveying accurate and relevant information about the study and its purpose; disclosing known risks, benefits, alternatives, and procedures; answering questions; and enabling the potential participant to make an informed decision about whether to participate.

General requirements for informed consent in federally funded research are spelled out in the *Code of Federal Regulations*, 45CFR.46.116. Certain states have additional statutes regulating research.

Elements of Consent

In order for consent to be valid, it should be based on the following critical elements:

- The participant must be COMPETENT to begin the informed consent process. If the participant is not competent because of age, illness, incapacity, or any other reason, special provisions apply, or the participant may not be included in the research.
- The research team must DISCLOSE all relevant information to the potential participant. The information must be sufficient to allow the potential participant to decide whether to participate. It is generally accepted that the potential participant must be given the following information: the purpose of the study; nature of the procedure; reasonable alternatives to the proposed intervention; and risks, benefits, and uncertainties of each possible intervention.
- The participant must COMPREHEND the information. The research team must evaluate the potential participant's ability to understand the proposed intervention in the study.
- The participant must AGREE to the proposed intervention in the research study.
- The participant's agreement must be VOLUNTARY and free from coercion.

Finally, participants must be informed that even after they have made a voluntary agreement to participate in the study, they may WITHDRAW such agreement at any time without penalty.

Preparing the Consent Document for IRB Review

The first step in the process of informed consent is preparing the written consent document for presentation to the IRB. This document should include all the elements listed in Table 1 in Appendix D (and required by 45CFR.46.116), as well as any other information prospective participants might need to make an informed decision about participation. Consent documents should be written in nontechnical language that can be understood by the proposed participant population—consistent with their educational level, familiarity with research, and cultural views.

The consent document must make clear that participation in research is voluntary, and it should not include any language waiving or appearing to waive participants' rights. In some cases, the researcher may want to request that the IRB approve a modification or waiver of the elements of informed consent as spelled out in the regulations.

Advertisements, fliers, or brochures prepared to recruit and inform potential participants about a study are considered part of the informed consent process and, as such, also require review and approval by the IRB.

Approaching Research Participants

Researchers and members of the research team are responsible for making sure that the process of informed consent conforms to the value of respecting individuals' right to make informed and voluntary decisions about research participation, as well as to the regulations guiding research with human participants. In this regard, after receipt of IRB approval of the consent plan, there are several essential steps to take in the process of informed consent. The researcher and responsible research team members should:

- Feel confident that the potential participant has the capacity to understand information, make decisions, and provide informed consent for the particular study.
- Provide both written (as described above) and oral information about the details of the study in a way that is understandable to the participant.
- Be satisfied that the participant understands the information provided and has had an opportunity to ask questions and deliberate about participation.
- Be satisfied that the participant is in a position to make a voluntary decision and has not been coerced or unduly influenced by circumstances or other people;
- Be satisfied that the participant agrees to participate, as indicated in most cases by signing an informed consent document.

How does the researcher determine if a participant has the capacity to consent?

Adults have the capacity to consent when they possess sufficient mental capability to understand the information provided, appreciate how it is relevant to their circumstances,

and make a reasoned decision about whether to participate in a particular study. Children (in most jurisdictions those under 18 years of age) do not have the legal capacity to consent independently.

Capacity can be affected by several things, including age, cognitive impairment, illness, and treatments. Capacity to consent for a study is study-specific. For example, a person may have sufficient capacity to carry out daily activities and make decisions, but not sufficient capacity to appreciate how the particulars of a given protocol might be relevant.

For some participants or groups of participants, the researcher or the IRB may decide that an independent capacity assessment is a good idea. This may involve consulting with a psychiatrist or neurologist to make a determination about an individual's cognitive ability and should include an independent assessment of the person's ability to understand the details and implications of the protocol being presented.

If a person is unable to provide his or her own consent, a legally authorized representative can in some cases give permission for participation in research. A legally authorized representative is a legal guardian; a parent (for children only); and in some cases, a validly designated durable power of attorney for health care (the latter is an evolving area). The researcher should check with institutional policies or assurance and the IRB.

What should the researcher consider when providing information to potential participants about the study?

The provision of information about a study usually involves more than just furnishing the written consent document to the potential participant to read. Oral presentation of information and the opportunity to discuss and answer questions and concerns are important parts of the process, usually in addition to giving the person time to read the written consent form. Educational materials about the study or clinical research in general are helpful. If the researcher delegates the function of oral presentation and discussion of a study to members of the team, he or she must be sure they have sufficient knowledge of the protocol to answer questions appropriately. Delegation may have to be approved by the institution's IRB.

How does the researcher assess the participant's understanding?

The researcher should feel satisfied that after the detailed information has been presented and discussed, the potential participant understands it well enough to make a decision. Of course, some studies are more complicated and involved than others. Researchers use many different strategies in determining whether or not a research participant understands. Sometimes it is clear at the end of a discussion; other times, having a participant answer questions about the study, either informally or even in writing, may be appropriate. The best method may depend on the complexity and risk level of the study as well as on the potential participants. For some studies, time to deliberate or discuss the study with family, trusted friends, or other health care providers can be very important.

How does the researcher know whether the participant's decision is voluntary?

Individuals who feel "coerced" into making a decision about research participation or are in a position in which it is impossible or extremely difficult for them to say "no" should not be enrolled into research. Coercion occurs if there is some threat of harm or punishment for refusal to participate. Individuals in relationships of unequal power or dependence have historically been particularly vulnerable to coercion. Examples might include telling students they would fail a course, employees they would not be promoted, or soldiers they would be reprimanded if they refused to participate in research. Coercion in research is rare due to the vigilance of research teams and IRBs.

All decisions, including decisions about research participation, are subject to the influences of one's previous experiences and circumstances. Sometimes, understanding an individual's reasons for considering participation is helpful in assessing how voluntary a decision is. The goal is to be sure that individuals understand research participation as a choice or an option among other—albeit in some cases, limited—options. Being sure that individuals understand that they can freely refuse to participate and/or withdraw at any time without penalty is critical to ensuring voluntary consent.

Must the researcher always obtain an individual's written signature?

In most cases, consent to research participation is documented by obtaining the signature of the participant or a legally authorized representative on the written informed consent document. A copy of this document should be given to the person signing the form. By Federal regulation, a signature is required on the written document containing all the required elements of information—or on a short form and written summary of the information when the information has been presented orally, as spelled out in 45 CFR.46.117(b)(2).

In some cases, a signed consent document is inappropriate. According to the Federal regulations at 45 CFR.46.117(c), the IRB may waive this requirement if it determines:

- There is a confidentiality risk, and the only link between the participant and the research would be the consent document.
- The research presents no more than minimal risk of harm and involves no procedures that normally require informed consent outside of research.

Consent by Proxy and Implied Consent

Proxy consent, or consent to participate in research by one competent adult on behalf of another, may be appropriate under certain circumstances. All uses of proxy consent must be approved by an institution's IRB.

If the prospective participant is identified as incompetent to provide informed consent, and if the condition of being incompetent is temporary, (if for example, potential participants have received sedating or pain-relieving medications and consent must be

obtained before the effects wear off), the duration of the incompetence is unknown (for example, when a potential subject is in a coma resulting from traumatic injury), or the potential participant is cognitively impaired, the subject's legally authorized representative is responsible for deciding whether the subject should participate in the research. This person will sign the consent form on behalf of the participant and will indicate his or her relationship to the subject.

Consent from the subject's legally authorized representative should be obtained by the researcher in person and documented on the approved consent form.

Consent provided by a proxy should never be accepted if the potential participant has indicated refusal to take part in the research.

Research with Children and Assent to Research

Legally, children have not attained an age at which they can consent to research or treatment. Therefore, special provisions for agreement to participate in research are established in Section 46.408 of the Federal regulations. This section establishes the requirements for obtaining permission from parents or guardians and assent from children. The parent or guardian may provide "permission" for the child to participate in a study. *Permission* means the agreement of parent(s) or guardians(s) to the participation of their children or wards in research. Valid permission can be given only following an explanation incorporating the information currently required for informed consent.

In most cases, the child must indicate willingness to participate by assenting to the study. *Assent* means a child's affirmative agreement to participate in research. By law, failure to object may not be construed as assent. IRBs make the final determination if sufficient protections exist for children and how assent should be documented.

The inclusion of children in research studies poses many ethical and legal questions. For further information, link to: http://grants.nih.gov/grants/guide/notice-files/not98-024.html.

Waiver of Consent

Federal law (see Title 45 CFR 46.116(d)) permits an IRB to waive the requirement of obtaining written prospective informed consent under the following essential conditions:

- The research poses no more than minimal risk to subjects.
- There are no adverse effects as a result of the waiver or alteration.
- Without the waiver or alteration, the research in question could not be carried out.
- Information will be provided after participation is completed, if appropriate.

Special Issues In Informed Consent

Language Barriers

Information relevant to participation in research must be communicated to participants "in language understandable to the subject," and in most situations, such informed consent must be documented in writing (45 CFR §46.116 and §46.117).

According to the statute [§46.117(b)(1)], the written consent document must include all elements necessary for legally effective informed consent in language comprehensible to the intended participants. Thus, participants who are not native English speakers should be provided with a consent document in their native language, written at a level that makes the information comprehensible.

The statute also provides for an alternative method of obtaining informed consent via oral presentation, accompanied by a short-form written consent document (stating the necessary elements and a written summary of what is presented orally). In that event, a witness to the oral presentation is required, and the participant must receive copies of the short-form document and the summary. The witness must be fluent in both languages.

Community Consent and Cross-Cultural Issues

Researchers conducting studies in multicultural settings have found that it sometimes is not enough to obtain individual consent using traditional concepts and rules. For example, among some ethnic groups, the role of the individual is secondary to the individual's role as part of a community, and there is no distinct concept of individual will or identity. In other groups, women will defer to the decisions of their husbands, fathers, or other male relatives and will not express their own wishes. In still other groups—and depending on the nature of the research—the implications of participating in research extend beyond the individual and affect the entire group or community.

Community may be defined as a group living in proximity, a group related by blood or marriage, or a group with a common religious, ethnic, or racial heritage or identity.

The concept of community consent has developed, largely in response to research involving identifiable groups. Research with these groups, which are sometimes related by blood as well as living in proximity, requires a reconsideration of traditional concepts of consent. Traditionally, consent was a private matter between an individual patient and a treating physician. Today, the implications of participation in research may involve information that affects family and community members as well. For example, members of one group may feel stigmatized if a number of members of that group participate in research that reveals unpopular or dangerous traits. This may be true for behavioral research that indicates certain behaviors (such as alcoholism or violence) that portray others in the community unfavorably. Moreover, the conduct of clinical research may

reveal general information that renders a group less desirable genetically, interfering with potential marriage prospects or employment opportunities.

As a result, some believe that community consent should be an additional requirement—or at least an issue addressed as part of education provided to participants—along with individual consent as a requirement for the ethical conduct of research.

Case Studies

Chapter 3 – Case Study 1

A young man (aged 23) comes to the medical center for possible participation in a novel high-dose chemotherapy study for a refractory tumor. He has been provided with the written consent document that contains all the informational elements required by the Federal regulations and approved by the IRB. He states that he has read the consent form and has no questions. Prior to obtaining his signature, the researcher discusses the study with him and offers to answer any questions he may have. In the course of this discussion, the researcher becomes concerned about how much of the study the young man actually understands. The researcher knows that the young man only has a 7th-grade education and is somewhat shy and uncommunicative.

The nurse begins to ask him questions about the study to assess his understanding. He can tell the nurse that he will be admitted to the hospital to receive a strong new drug that might make him very sick while he is in the hospital but that might also help his cancer. He also explains that he thinks the only other choice available to him is amputation of his arm. Upon further questioning, he says that he understands the study is trying to find out if this drug works in him and other people like him, and that there is no guarantee that it will help him.

He cannot, however, provide the name or dose of the drug or describe how it will be given or how it is believed to work. He can remember a couple of the possible side effects, but not the majority of them (there is a long description of risks, about three pages, in the consent document). He cannot describe parts of the study that are purely for research, such as additional scans or the storage of tissue for analysis of tumor characteristics and future studies.

In your judgment, is he ready to sign the consent document? Are there other things that might be helpful before you proceed with asking him to sign the consent document?

The following are things that might be helpful before asking him to sign the consent document:

- Giving him additional time to deliberate and discuss the study with other members of the research team or members of his family

- Consulting with another resource (a psychiatrist, ethics consultant, social worker, or small interdisciplinary group) to evaluate either his capacity to give consent, his understanding of this particular study, or both
- Holding a group discussion among the research team regarding the adequacy of his understanding of the study
- Explaining the study specifics again, especially the areas that are crucial to his understanding and participation
- If it is suspected that other possible participants might have difficulty understanding the details of the study, developing pictures, a video, or some other visual explanation of the study

Chapter 3 – Case Study 2

A group of investigators proposes a long-term prospective study of recent-onset Alzheimer's disease. The study involves a large group of middle-aged adults. The investigators are developing the informed consent document and have concerns regarding the capacity of the participants to consent both when enrolled and for the duration of the study.

Q. If the participants are judged unable to provide informed consent, from whom should consent be obtained?

A. The investigators have a duty to identify a legally authorized representative of the potential participant in order to obtain valid consent. According to the Common Rule, *legally authorized representative* means an individual, judicial body, or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

In general, and depending on the law of the state, the *legally authorized representative* need not be appointed by a court. However, the investigators do have an obligation to identify another individual who can consent on behalf of the participant.

The investigators should first contact the spouses of potential participants. If a potential participant is not married but has adult children, these children should be contacted. In the absence of adult children, other relatives may be asked to give consent.

Note that some state laws specify who may be considered a legally authorized representative in making treatment, but not research, decisions.

Chapter 4: IRB Review

This chapter defines the basic terms used in the Federal guidelines and regulations protecting participants in research. Understanding who is the research participant and when a research study includes human participants guides the researcher and team in applying the appropriate policies. The roles and responsibilities of the researcher and the team in relation to human participant protections are explored.

In this Chapter, the following topics will be discussed:

- **History of IRB Review**
- **Roles & Responsibilities of the IRB**
- **IRB Membership**
- **Criteria for IRB Approval of Research**
- **Assessment of Risk & Benefits**
- **Types of IRB Review**
- **Research Exemptions from IRB Review**
- **Case Study**

Learner Objectives

- Define *institutional review board* (IRB), describe its membership requirements, and identify at least four responsibilities of an IRB
- List the criteria each study must meet in order to be approved by an IRB

History of IRB Review

In response to the revelations of the Tuskegee Syphilis Study (1932–1972), the Department of Health, Education, and Welfare (DHEW) appointed a panel to review the study as well as the Department's policies and procedures for the protection of human participants in general. The panel concluded that Congress should establish "a permanent board with the authority to regulate at least all federally supported research involving human subjects." In 1974, Congress passed the National Research Act, which required the establishment of institutional review boards (IRBs) to review all DHEW-funded research. The Act also created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which issued the Belmont Report, the seminal document that provides the ethical principles upon which current protections of research participants are based.

Also in 1974, DHEW (subsequently, DHHS) established regulations for the Protection of Human Subjects of Biomedical and Behavioral Research that included the framework for IRB review procedures (45 CFR 46, Subpart A). These procedures were revised in 1981 in response to recommendations of the National Commission that delineated more

carefully the IRB requirements, responsibilities, and procedures IRBs were required to follow.

In 1991, to provide unity within the human protections system, the core DHHS regulations (Subpart A) were formally adopted by 17 departments and agencies, representing most, but not all, Federal departments and agencies sponsoring human research. Subpart A subsequently became known as the "Common Rule." Research involving fetuses or pregnant women, prisoners, or children is governed by special provisions (45 CFR 46 Subpart B, Subpart C, and Subpart D, respectively).

The Food and Drug Administration (FDA) has separate regulations and policies concerning IRB review as set forth in 21 CFR 56. The basic requirements for IRBs and for informed consent are congruent between the two sets of regulations.

Roles and Responsibilities of the IRB

An IRB protects the rights, safety, and welfare of human research participants by:

- Reviewing the full protocols for planned research studies to ensure that, in its judgement, the research meets the criteria found at 45 CFR 46.111.
- Confirming that the research plans do not expose participants to unreasonable risks.
- Conducting continuing review of approved research at intervals commensurate with the degree of risk of the trial, but not less than once a year, to ensure that human participant protections remain in force.
- Considering adverse events, interim findings, and any recent literature that may be relevant to the research.
- Assessing suspected or alleged protocol violations, complaints expressed by research participants, or violations of institutional policies.

The IRB has the authority to:

- Approve, disapprove, or terminate all research activities that fall within its local jurisdiction according to relevant Federal regulations and institutional policy.
- Require modifications in protocols, including previously approved research.
- Require that information, in addition to that specifically mentioned in 45 CFR 46.116, be given to participants when the IRB determines that this information would add to the protection of their rights and welfare.
- Require documentation of informed consent or allow waiver of documentation, in accordance with 45 CFR 46.117.

For more information on the roles and responsibilities of the IRB, see 45 CFR 46.109.

IRBs are charged with evaluating research studies in terms of the risk the research poses to human participants (subjects) and with reviewing the informed consent process

according to the level of risk posed. If the research involves no greater than minimal risk, the study must be reviewed by an IRB but may be eligible for expedited review (review of proposed research by the IRB Chair or a specified voting member, rather than by the entire IRB).

Expedited Review

The DHHS human subjects regulations at 45 CFR 46.110(b)(1) limit the use of expedited review procedures to specific research categories published in the *Federal Register* at 63 FR 60364-60367 (see http://ohrp.osophs.dhhs.gov/humansubjects/guidance/expedited98.htm), and to the review of minor changes in previously approved research during the period (1 year or less) for which approval is authorized. IRBs are permitted to use expedited review for the continuing review of research that involves solely activities published at 63 FR 60363-60367. If the risk to the subjects is greater than minimal, full IRB review is warranted. Generally, if research did not qualify for expedited review at the time of initial review, it does not qualify for expedited review at the time of continuing review, except in limited circumstances described by expedited review categories (8) and (9) at 63 FR 60364-60367. It is also possible that research activities that previously qualified for expedited review in accordance with Section 46.110 have changed or will change such that expedited review would no longer be permitted for continuing review.

Office for Human Research Protections

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks, is part of the Office of the Secretary, Department of Health and Human Services. OHRP is responsible for interpreting and overseeing implementation of the regulations regarding protection of human subjects as described in Title 45, Part 46 of the *Code of Federal Regulations*, and its Subparts A–D. OHRP has oversight and educational responsibilities wherever DHHS funds are used to conduct or support research involving human participants, and when the research institutions have included all research they conduct in their Assurances filed with OHRP, regardless of funding source. The OHRP Web site is http://ohrp.osophs.dhhs.gov/.

Filing an Assurance

According to DHHS regulations 45 CFR 46.103, every institution engaged in human subjects research supported or conducted by DHHS must obtain an assurance of compliance approved by the Office for Human Research Protections (OHRP). Until recently, OHRP reviewed and approved many types of assurances from institutions. The three most common were: Multiple Project Assurance (MPA) for Federalwide use, Cooperative Project Assurance (CPA), and Single Project Assurance (SPA). Since December 2000, OHRP has encouraged each institution engaged in DHHS-supported or DHHS-conducted human subject research to submit a new and simplified assurance document, termed the Federalwide Assurance (FWA). The FWA Signatory Official must be authorized to represent and commit the entire institution and all its components

to a legally binding agreement. (See definition of *engaged* at http://ohrp.osophs.dhhs.gov/humansubjects/assurance/engage.htm)

The OHRP has also developed an Institutional Review Board (IRB) registration system. Registration of an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) with the OHRP is voluntary; however, IRB/IEC registration is required for any IRB/IEC designated on an FWA. IRB registration is not currently mandatory according to the Food and Drug Administration.

IRB Membership

IRBs comprise sufficiently qualified individuals who have no vested interest in the research study or its outcomes. Their responsibility is to ensure that all research studies are ethical and justified.

Federal regulations mandate that an IRB have at least five members with varied backgrounds, although it may have as many members as necessary to perform a complete and adequate review of research activities. Membership should be diverse regarding race, gender, cultural heritage, and sensitivity to issues such as community attitudes to promote respect for its advice and counsel in safeguarding the rights and welfare of research participants. If the IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or physically or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects. In addition, it should be noted that other requirements for IRB membership at 45 CFR 46.107 (b) – (f) also apply.

If an IRB reviews research that involves vulnerable populations, such as children, prisoners, pregnant women, or disabled or cognitively impaired persons, the IRB should include one or more persons who are knowledgeable about and experienced in working with these populations.

No IRB may consist entirely of members of one profession; each IRB should include at least one member whose primary concerns are in scientific areas and one member whose primary concerns are in nonscientific areas. Each IRB should include at least one member not affiliated with the institution. No IRB may have a member participate in the IRB's review of any project in which that member has a conflicting interest, except to provide information requested by the IRB.

The IRB may invite individuals with competence in special areas to assist in the review of issues that require expertise beyond or in addition to that of the IRB members. These individuals are not voting members.

Criteria for IRB Approval of Research

In order to approve research, the IRB must ensure that the following requirements are satisfied:

- Risks to participants are minimized by using procedures consistent with sound research design that do not unnecessarily expose participants to risk.
- Risks to participants are reasonable in relation to anticipated benefits, if any, to participants, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those that may result from the research, as distinguished from those participants would receive even if not participating.
- Selection of participants is equitable. The IRB should consider the purposes of the research and the setting in which the research will be conducted and be particularly mindful of the special problems of research involving vulnerable populations. Participants should share equally in foreseeable benefits and risks.
- Informed consent is sought, and will be obtained, from each prospective participant or the participant's legally authorized representative in accordance with, and to the extent required by 45 CFR 46.116.
- Informed consent is appropriately documented in accordance with, and to the extent required by 45 CFR 46.117.
- When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of participants.
- When appropriate, there are adequate provisions to protect the privacy of participants and to maintain the confidentiality of data.
- Additionally, when some or all of the participants are likely to be vulnerable to coercion or undue influence (e.g., children, prisoners, pregnant women, or mentally disabled, economically disadvantaged, or educationally disadvantaged persons) additional safeguards are included in the study to protect the rights and welfare of these participants.

Assessment of Risks and Benefits

When approving research, the IRB must assess whether the anticipated benefit of the research—either new knowledge or improved health for the research participants—justifies inviting anyone to undertake the risks. The IRB should not approve research in which the risks are judged unreasonable in relation to the anticipated benefits.

Risks to individuals are classified as physical, psychological, social, legal, and economic. In the process of determining what constitutes a risk, only those risks that may result from the research, as distinguished from those associated with therapies participants would undergo even if not engaged in research, should be considered.

Once risks have been identified, the IRB must assess whether the research poses minimal or greater than minimal risk. *Minimal risk* (defined in 45 CFR 46.102) is defined such

that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

The concept of *minimal risk* is used in the Federal policy for three purposes. First, the concept guides the IRB to determine if the proposed research should be reviewed by the entire Board or if it may qualify for expedited review. Second, it is used to determine what research can proceed without consent, and third, the concept is used to decide when documentation of subject consent may be waived.

IRBs must ensure that risks to participants are minimized. Researchers should include strategies for reducing risks in the protocol. For example:

- Precautions, safeguards, and alternatives should be incorporated into the protocol to reduce the probability of harm or to limit its severity or duration.
- IRBs should determine whether the researchers are competent in the planned area and whether they serve dual roles (e.g., as clinician and researcher) that may result in conflicts of interest and lead to a "therapeutic misconception" being held by the research participant.
- IRBs should assess whether the research design will yield useful data, so that research participants are not exposed to risks without sufficient justification.

The IRB must be notified of any unanticipated problem involving risks to participants or others, including physical or psychological injury to participants, improper disclosure of private information, economic loss, or other potentially harmful occurrences.

Types of IRB Review

Depending on the level of risk of the research protocol and the participant population, IRBs may conduct either full board review or expedited review.

Expedited Review

For certain kinds of research involving no more than minimal risk, and for minor changes in approved research, the IRB Chair or a designated voting member or group of voting members review the proposed research rather than the entire IRB. It cannot be assumed that research poses minimal risk because it involves only interview or survey data collection. Sensitive questions may lead to distress that exposes participants to greater than minimal risk. Loss of confidentiality can cause harm to participants, their relatives, and others.

Full Board Review

When *full board review* is necessary, the research proposal is presented and discussed at a meeting at which a quorum of IRB members is present. For the research to be

approved, it must receive the approval of a majority of those voting members present. (Note that, in effect, an abstention counts as a negative vote.)

Research Exemptions from IRB Review

Under Federal regulations [45 CFR 46.101 (b)], certain categories of activity are considered research but may be declared exempt from review by the IRB. This determination should be made by someone other than the Principal Investigator, and may be confirmed by the IRB.

Certain low-risk research is exempt from the requirements in the Federal regulations concerning IRB review and approval. If a study falls into one of the exempt categories, researchers still have ethical responsibilities to protect participants' rights. The researcher should not make the final determination of exemption from the applicable Federal regulations or the provisions of the institution. Researchers should check with their institution's guidelines or IRB policies to determine who will make the determination of exemption for a proposed study.

The following are the six exempt categories as listed in 45 CFR 46.101(b):

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices
2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior, unless:
    a. Information obtained is recorded in such a manner that human participants can be identified, directly or through identifiers linked to them.
    b. Any disclosure of the human participant's responses outside the research could reasonably place the participant at risk of criminal or civil liability or be damaging to the participant's financial standing, employability, or reputation.
3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (2) of this section, if:
    a. The participants are elected or appointed public officials or candidates for public office.
    b. Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information be maintained throughout the research and thereafter.
4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the researcher in such a manner that participants cannot be identified, directly or through identifiers linked to them

5. Research and demonstration projects conducted by or subject to the approval of Federal department or agency heads and designed to study, evaluate, or otherwise examine public health benefit or service programs
6. Taste and food-quality evaluation and consumer acceptance studies

These exemptions do not apply to research involving prisoners, fetuses, pregnant women, or newborns. Further, the exemption in item 2 above does not apply to children, except in research involving observations of public behavior when the researcher(s) do not participate in the activities being observed. Interviews, surveys, and interactive observations are not exempt, while educational tests and noninteractive observations are.

Note that when research is conducted in countries outside the United States by foreign Principal Investigators, the rules for IRB review and exemption may differ if the bases for the institutional assurances are founded upon documents other than the Belmont Report and the Common Rule. Note that research conducted in countries outside the United States by U.S.-based Principal Investigators is not affected by this potential modification. Researchers should review the section covering international research for further information and always consult with their institution's IRB.

Case Study

Chapter 4 – Case Study

Investigator Y is studying aggressive behavior exhibited by elementary school children in the classroom. The objective of the research is to study the development of conduct problems and violent behavior in children. The Investigator wishes to observe children in the classroom, videotape the interaction, and analyze the behavior exhibited.

The Investigator is drafting a protocol for IRB review and preparing the informed consent documents for submission to the IRB.

Q. From whom must consent be obtained?

A. The investigator should obtain approval from the school principal and informed consent from the classroom teacher. Written permission must be obtained from the participating children's parents. In addition, the children must give their assent after being told about the research study.

Q. Should the research team obtain written permission from both parents? Or is it acceptable to obtain permission from only one parent?

A. As long as the risks are judged to be minimal (by the local IRB), informed consent may be obtained from one parent.

Q. What can the Investigator do if the parents of a particular child do not give their consent?

A. The investigator may take any of the following steps if consent is not obtained from the parents of an individual child.

- Cancel the study.
- Redesign the study to include a smaller group of children.
- Coordinate with the school and parents so that the child is not present when the observation occurs.

Chapter 5: Ongoing Protections

The researcher and team's obligation to protect human research participants does not end with initial approval of the study or a signed informed consent document. In clinical research, the commitment to participants is to safeguard their interests throughout the study.

These commitments (for example, appropriate clinical monitoring, management of adverse events, and treatment of injuries) are written into the informed consent document. An ongoing challenge is the need to reassess the balance between risks and benefits, both to the participant and, in some genetic research, to the participant's family, as new information becomes available. This chapter includes methods to protect human research participants during the conduct of the study.

In this Chapter, the following topics will be discussed:

- **Ongoing Informed Consent**
- **Adverse Event Reporting**
- **Ongoing Data & Safety Monitoring**
- **Continuing IRB Review**
- **Case Study**

Learner Objectives

- List and describe four ways that ongoing protections of human participants are ensured throughout the conduct of a study

Ongoing Informed Consent

Informed consent is communication process that continues during the entire study. Many of the elements of informed consent previously discussed apply throughout the study. See Table 1 in Appendix D to refresh your memory about these elements. The researcher and research team should:

- Feel confident that the participant maintains the ability to understand information, make an informed decision, and voluntarily continue to participate.
- Provide written and oral information about emerging study details in a manner understandable to the participant.
- Be satisfied that the participant understands the information provided, has had an opportunity to discuss the information and ask questions, and understands that he or she may withdraw from the study at any time.

When changes in the study occur, and/or significant new findings develop during the course of the study that may affect the participant and his or her willingness to continue

participation, additional informed consent may be necessary. Continuation of the study may require having participants sign a new consent form (obtaining reconsent). All proposed changes in the protocol and the consent must be submitted to the IRB. Researchers should consult their IRBs for the requirements for study changes and reconsent procedures.

Adverse Event Reporting

Federal regulation (21 CFR Part 312) defines "adverse event" as any untoward medical occurrence that may present itself during treatment or administration with a pharmaceutical product, and which may or may not have a causal relationship with the treatment.

Studies conducted with an investigational agent or device (IND or IDE) are subject to the requirements of 21 CFR part 312 as well as 45 CFR 46, Subpart A (Research involving human subjects). The FDA rules also include specific reporting requirements when adverse events occur. The researcher and team are responsible for reporting any adverse events to the IRB, study sponsor, NIH, and FDA (according to 21 CFR 312.32). The researcher and team should be familiar with IRB policies, adhere to these policies, and maintain a copy of these policies in the research study file. The researcher is also responsible for accurate documentation, investigation, and follow-up of all possible study-related adverse events.

Careful adverse event reporting means reporting in a timely manner. Safety problems must be identified and reported to the IRB, appropriate institutional officials, the FDA (if the researcher sponsors the IND or IDE for the agent or device) and the NIH in a manner outlined in the protocol.

For further guidance in reporting adverse events to the IRB for NIH-supported multicenter clinical trials, see http://grants.nih.gov/grants/guide/notice-files/not99-107.html.

The data and safety monitoring plans required for all federally funded research studies must include a description of the reporting mechanism should an adverse event occur. Generally, the NIH Institute or Center funding and/or sponsoring the IND for the agent establishes operational definitions of adverse events that can be applied to its sponsored studies and specific reporting mechanisms. For example, the National Cancer Institute (NCI) defines *adverse events* in its clinical trials involving investigational agents as:

> Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of *unrelated, unlikely, possible, probable,* or *definite*).

(See the Web site: http://ctep.cancer.gov/reporting/adeers.html)

If the study includes an investigational agent or medical device, the research team must adhere to both the NIH and FDA policies and regulations for adverse event reporting.

The FDA, in Federal Regulations 21 CFR 312.32, defines *adverse event* as any untoward medical occurrence that may present itself during treatment with or administration of a pharmaceutical product, and which may or may not have a causal relationship to the treatment. In the guideline entitled *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*, the FDA further clarifies and defines *serious adverse events* stemming from a study involving an investigational agent as any untoward medical condition that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, or creates persistent or significant disability/incapacity or a congenital anomaly/birth defect. The FDA also has specific reporting procedures. The research team should adhere to the policy and procedures of the IND sponsor for adverse event reporting as required by FDA regulations.

Ongoing Data and Safety Monitoring

Data and safety monitoring plays an essential role in protecting the safety of participants and ensuring integrity of the research study.

The objectives of data and safety monitoring are to:

- Ensure that risks associated with research participation are minimized to the extent practical and possible.
- Avoid exposure of participants to excessive risk.
- Ensure data integrity.
- Stop a study: (1) if safety concerns arise; or (2) as soon as the study objectives have been met.

Monitoring should be commensurate with risks and with the size and complexity of the research. The NIH requires data and safety monitoring in the form of a Data and Safety Monitoring Board (DSMB) for multicenter Phase II clinical trials involving interventions that entail potential risk to the participants, and individual institutes and centers may require then for other types of trials as well.

The DSMB is an independent committee whose members include, at a minimum, a biostatistician and a clinical expert in the area being studied. Members should have expertise in all scientific disciplines needed to interpret the data and ensure participant safety. The committee may also include clinical trial experts and bioethicists.

DSMB members protect the safety of participants by being familiar with the study, proposing appropriate analysis, and periodically reviewing the developing outcome and safety data. The DSMB ensures the integrity of the study by reviewing data on such

aspects as participant enrollment, site visits, study procedures, forms completion, data quality, losses to follow-up, and other measures of adherence to protocol. The DSMB monitors adverse events, discusses concerns in this regard, and makes recommendations regarding appropriate study and operational changes. The DSMB monitoring function is above and beyond the oversight traditionally provided by the IRB and, as such, is particularly important for multicenter research studies.

For those Phase I and Phase II trials for which the establishment of a DSMB is not required, researchers must submit a general description of the data and safety monitoring in a written plan. This data and safety monitoring plan is developed by the researcher and is trial-specific. It must be included as part of the protocol and submitted to the local IRB. It is also reviewed and approved by the Institute or Center funding and/or sponsoring the IND or IDE for the agent or device before the trial begins.

All data and safety monitoring plans must include, at a minimum, a description of the reporting mechanism of adverse events to the IRB, the study sponsor, appropriate institutional officials, the FDA (if the researcher sponsors the IND or IDE for the agent or device), and NIH. Other issues that may be addressed include enrollment, retention, adherence, data completeness, safety, and efficacy. Researchers must ensure that the NIH is informed of any actions taken by the IRB as a result of safety monitoring reviews.

NIH policy and guidance for data and safety monitoring can be found at:

http://grants.nih.gov/grants/guide/notice-files/not98-084.html

Additional guidance and examples for preparing DSMB plans may be found at: Data and Safety Monitoring Example Plans. This site presents examples of NCI-approved Institutional Data and Safety Monitoring Plans that were submitted by NCI-designated Cancer Centers in response to the NIH and NCI policies.

Key points to remember about data and safety monitoring:

- Data and safety monitoring must occur periodically throughout each study.
- Periodic data summary reports are developed to determine if the study should change in any way or stop. Any resulting significant changes are implemented with the approval of the local IRB and are reported to appropriate institutional officials, the study sponsor, the FDA (if the researcher sponsors the IND or IDE for the agent or device) and NIH.
- The risk/benefit ratio must be reassessed based on any new internal or external data and information.

Continuing IRB Review of Ongoing Studies

Review of studies by the IRB on not less than an annual basis allows it to determine if there are any study-related events that endanger currently involved study participants or those who have completed the study. If so, the IRB may require notification of participants, change to the informed consent, or cessation of the study with notification given to all participants. With a DSMB in place, the IRB can review written summary reports from the researcher after DSMB review. In multisite studies, this is particularly important, as each site's IRB often will not receive individual adverse event reports from sites other than its own.

Case Study

Chapter 5 – Case Study

This study is an NIH-sponsored (sponsoring the IND for the investigational agent) Phase III, multisite clinical trial comparing a four-drug combination of antiretroviral drugs to a three-drug combination. The objective is to ascertain whether, on average, the new four-drug combination can delay virologic progression of disease in HIV-infected persons. The four-drug combination consists of the three-drug combination plus an investigational drug, so the trial is a test of whether the new drug adds benefit. The trial will require the enrollment of several hundred volunteers and is expected to take as long as 2 years. Treatment for each participant will continue using the initially assigned drug combination until there is clear evidence that the participant is not benefiting. The safety profile of the three-drug combination is fairly well established from past studies, as is the safety profile of the new drug when given by itself to less ill persons than those who will enroll in the study. Very little is known about how the new drug might interact with the older combination to possibly produce different kinds of problems.

Based on this case, consider the following scenarios:

- A few months after starting, there have been reports of pronounced anemia in five participants taking the new drug combination and none in participants taking just the three-drug combination.

  Q: To whom should you report these results?

  A: The research team must follow the data and safety-monitoring plan as written in the protocol. According to Federal policy for adverse events, these findings should be reported to the DSMB, IRB, study sponsor, NIH (appropriate Institute or Center) and the FDA, (if the researcher sponsors the IND or IDE for the agent). The other sites will need to be notified as required by the FDA.

- (Assuming the study continues) Later, but still before study recruitment finishes, a summary of study results reveals that participants in the four-drug group have better outcomes than expected, and the observed difference is statistically significant.

  Q: What might happen to your study?

  A: The DSMB has the responsibility to review interim statistical reports based on the data and safety monitoring plan set forth in the protocol. It is possible that the study would be stopped and participants notified of the results and all participants be offered the more effective drug combination.

Chapter 6: International Research

The researcher and team's obligation to protect human research participants does not end with initial approval of the study or a signed informed consent document. In clinical research, the commitment to participants is to safeguard their interests throughout the study.

These commitments (for example, appropriate clinical monitoring, management of adverse events, and treatment of injuries) are written into the informed consent document. An ongoing challenge is the need to reassess the balance between risks and benefits, both to the participant and, in some genetic research, to the participant's family, as new information becomes available. This chapter includes methods to protect human research participants during the conduct of the study.

In this Chapter, the following topics will be discussed:

- **Background**
- **Compliance with U.S. Laws and Policy**
- **Office for Human Research Protections**
- **Informed Consent**
- **Protecting Participants**
- **Case Study**

Learner Objectives

- List and describe special challenges to investigators that may arise when conducting international research
- Describe the regulations and policies applicable to international research supported by U.S. federal monies.

Background

International Research

Research projects conducted at various sites outside the United States present numerous issues that demand ethical review. Countries differ widely in their approaches to treatment of women and minorities, the role of children, the amount and quality of information disseminated to the people by the government, and access to medical care. When there is a discrepancy between the values and economic power of the sponsoring country and those of the country in which the research occurs, special care must be taken to ensure that research is conducted at the highest ethical standard.

Protection of human participants is as important in international research as it is for research in the United States. However, ensuring protection requires special attention

and consideration. The identification of communities and individuals for participation in research, the process of obtaining valid informed consent, and the completion of ethical review by an IRB or research ethics committee often poses special problems. Moreover, particular ethical concerns arise with regard to study design and choice of intervention (particularly when the standard of care in the host country differs from that of the sponsor), access to health care, and cross-cultural issues.

Compliance with U.S. Laws and Policy

Investigators who conduct research supported by U.S. Federal monies must comply with U.S. Federal regulations governing the protection of human subjects even when the study is conducted outside the United States. Specifically, the Common Rule applies to federally funded human research (unless exempt), and according to the Common Rule, informed consent must be obtained or waived, and there must be appropriate review and approval of each study.

Office of Human Research Protections (OHRP) and International Research

When research is funded wholly or in part by the U.S. Department of Health and Human Services (which includes the NIH), the foreign institution must file an assurance of compliance with U.S. regulations with the Office of Human Research Protections (OHRP). Further information about obtaining an assurance can be obtained from the OHRP at the following Web site: http://ohrp.osophs.dhhs.gov/irbasur.htm

OHRP will consider international codes and the protections proposed when reviewing the application for Federalwide Assurance (FWA). In general, the Assurance includes specific procedures in addition to a general assertion of compliance with U.S. regulations and international codes for protection of human participants. Most of the time, an Assurance indicates in writing that the study will be reviewed and approved by a duly constituted IRB or research ethics committee in the host community.

Equivalent Protections

Federal regulations permit approval of research in foreign countries when "the procedures prescribed by the [foreign] institution afford protections that are at least equivalent to those provided in this policy" [45 CFR 46.101(h)]. OHRP is developing procedures for evaluating "equivalent protection." If found to be equivalent, the foreign country's procedures for protecting human subjects may be substituted for the Common Rule.

Informed Consent

Most regulations and codes of research ethics require the voluntary informed consent of capable adults asked to participate in research. In the context of international research, the process of informed consent becomes more challenging for several reasons, including: the problem of disclosing scientific and medical facts to individuals who are unfamiliar with, and sometimes distrust, the concepts; differences in cultural and societal norms; and potential differences in the role of women in society or the role of the family and community in the consent process.

Other cultures hold different concepts of the nature of disease and health, and this framework may be a barrier to communicating the nature of the condition or disease under study or the nature of the research. Researchers should indicate awareness and sensitivity to culturally appropriate ways to disclose information pertaining to research, its risks and potential benefits, research design, and any post trial benefits.

Researchers in foreign countries will frequently encounter multiple local languages, varying levels of literacy, and specific religious or ethnic customs that may have to be taken into account when obtaining informed consent for research.

The Role of the Family or Community in the Consent Process

Investigators may encounter a situation where permission to conduct research may first be needed from community leaders or senior family members. The NIH encourages investigators to respect local traditions and cultural beliefs; however, the principle of respect for autonomy requires the individual consent of an adult for most research. Although individual consent may not be replaced, it could be supplemented by the consent of another individual in that community or consent of the group.

If the proposed research involves women or children, members of the immediate family may need to be consulted prior to beginning the study. A process in which a woman's consent is supplemented by consent of other (male) family members may be appropriate under certain circumstances. However, it is not acceptable to use different consent procedures for men and women. Special provisions may have to be included to allow a woman to choose not to participate without risking repercussions from her spouse or other community leaders.

Protecting Participants

Protecting Participants: Selection of a Population and Research Design

Few issues in international research have been as controversial as the selection of an ethically and scientifically appropriate research design. This is especially difficult in

settings with limited health care resources. Controversy has arisen when the proposed research design is different from what might be acceptable in another country.

In all research, the potential benefits of the research must outweigh the risks to participants. This principle is the essence of ethical research. Internationally, it is generally agreed that research should be designed and conducted so that it is responsive to the health needs and priorities of the population of participants. Each proposed study should demonstrate how it is responsive to those needs and how it can provide some benefit to the host community. Decisions regarding what population to include and what design to employ should be justified on this basis.

Furthermore, when deciding on an appropriate research design, access to health care, choice of controls, and the relationship of the design to the prevailing standard of care should be addressed and adequately discussed in the protocol. The involvement of host-country persons on the research team and oversight committees is encouraged and may be regarded as an indication that local concerns are being addressed.

Protecting Participants: Post Trial Benefits

An additional factor to consider prior to conducting research on a particular group is how research on the disease or condition under study will provide future benefit to that population. For example, certain populations may not benefit from research findings if a particular treatment is prohibitively expensive and, hence, unavailable. Consideration of how tested interventions might be made available after the research is concluded can be important in addressing this ethical concern.

Because of the complexity of the issues involved coupled with limited experience in implementing standards for the ethical conduct of research in international studies, investigators will be asked to justify their decisions with a high level of detail to demonstrate the connection between the design and protection of human participants.

Case Study

Chapter 6 – Case Study

An NIH-funded study has been approved to evaluate a new drug for the treatment of malaria. The study is to be conducted in a West African country among a population in which malaria is endemic. The study has been funded for 4 months.

Currently, malaria is treated with oral therapy based on one of three drug regimens: Quinine sulphate (common side effects include tinnitus, high-tone hearing loss, nausea, and dysphoria); atovaquone in combination with proguanil (very expensive); or Mefloquine (side effects include risk of vomiting).

New treatments are in demand to address drug resistance and the side effects. The study involves testing a new treatment and comparing it with established malaria therapy.

Q. What is the obligation of the investigators with regard to the host population at the conclusion of the study?

A. The investigators should consider and propose a mechanism for addressing posttrial access to medical care. The investigators should consult with community leaders prior to the study to discuss an effective plan. Such a plan should address the health needs of the general local population, as well as those of trial participants.

Appendix A: Current Issues

As you have learned in the previous sections, current events and issues in society, science, and research have stimulated governments to regulate research activities to protect human participants. In the United States, federal regulations and policies have been developing since the 1960s and continue to expand as new fields of science and research create demand for increased numbers of humans to participate in research studies. Today's rapidly developing fields of molecular biology and information technology have heightened public concerns and fostered public debate about a number of complex public issues related to human participant protection. Major issues include:

- **Human Genome Research and Hereditary Illnesses**
- **Behavioral Research**
- **Research Using Human Biological Material**
- **Public Awareness of Research**

Human Genome Research and Hereditary Illness

Human genome research is beginning to provide researchers with information regarding the genetic makeup of individuals, especially regarding the potential of a person to develop certain diseases. However, the relationship between having a certain gene and developing a disease is very complex and influenced by many factors. Mapping the details of the human genome provides a template for understanding the role of specific genes in disease, and the complicated task ahead will be translating this information into knowledge.

Researchers are still years away from fully understanding the relationship of risk of disease development to genetic makeup, and probably decades away from developing interventions based on genetic risk or molecular therapies. Ethical issues can arise concerning the participant's right or need to know research data, especially genetic data, if the future health implications of such information are not well understood. The researcher's understanding of regulations regarding informed consent are critical in helping scientists understand their responsibilities and in protecting human rights of research participants.

Research on hereditary illnesses presents a unique set of issues insofar as it may reveal information that is potentially important and/or troubling to family members of research participants. In particular, care should be taken to respect participants' privacy and the confidentiality of research findings. Preliminary information about genetic markers must be validated and carefully interpreted and not used to provide participants with individual results. Family members of research participants are generally not considered human subjects (participants) with respect to research studies; however, this issue is being considered by various bodies in the bioethics field. There are many state laws addressing specific provisions for valid research, and some states mandate certain requirements with

respect to informing participants if and when genetic tests are performed, describing prohibitions on discrimination in provision of employment or insurance, and obtaining or providing informed consent.

Behavioral Research

Behavioral research, the study of human behavior, serves as an important source of medical and non medical information. Research in this area presents its own ethical dilemmas, especially insofar as certain behaviors may be associated with social or cultural stigmas. Behavioral research in the area of health includes basic behavioral research as well as research on the etiology, prevention, and treatment of disease and the development, testing, and dissemination of disease prevention information and health promotion. Diet, exercise, lifestyle, alcohol consumption, drug use, sexual behaviors, etc. are all examples of the types of behavior that may be studied by investigators, highlighting the importance of protecting the privacy of research participants.

Research Using Human Biological Material (Tissue Research)

Researchers have used human biological materials (tissue, cells, blood, etc.) for years in the pursuit of knowledge about disease diagnosis, prevention, and treatment. New technologies and advances in biology and genetics have spurred interest in analyzing these materials using new tests with far-reaching potential. A number of ethical questions surround these tests, including whether it is appropriate to use archived tissue for tests that were not anticipated at the time of original collection. Issues pertaining to the nature and scope of informed consent and the permitted uses, including future uses of newly collected tissue, are important to the ethical conduct of research. One emerging line of analysis in this area is the identifiability of stored tissue. In general, legal and ethical standards refer to the type of tissue, the proposed use, whether the tissue is identified, and the method of identification.

Patient and Public Awareness of Research

In general, due to the increased use of the Internet and national news coverage of research results on new drugs and medical technologies, the public is currently more aware of research. Both the proliferation of media attention and increased public awareness of biomedical research heighten the importance of the research community's continued commitment to protecting the rights of human participants, thus maintaining the public trust.

Case Studies

Appendix A – Case Study 1

Investigators wish to study an association between a particular gene and shyness. They have designed a study as follows: Research is to be performed on a cohort of second-grade children from a large public school. The children will be observed in the classroom by the research team, and samples of their saliva will be collected for genetic analysis.

Q. What are some of the risks of this research?

A. The children's privacy may be violated when their classroom behavior is observed.
Children who are identified as "shy" may be stigmatized.

Q. What other issues should be considered by the research team?

A. Are there state laws governing genetic testing or use or disclosure of genetic information?
What will be done with genetic samples at the conclusion of the study?

Appendix A – Case Study 2

The following case study illustrates the definitions used to determine if study of specimens is considered human participant research and a possible exemption from IRB review.

A highly respected researcher at Outstanding University in Montana is conducting studies on markers of cancer progression. Dr. Respected is ready to initiate a new set of experiments using tissue specimens from patients with early-stage breast cancer. To carry out these studies requires access to archival breast cancer specimens not available from the local pathologist. Since she will not have sufficient specimens, Dr. Respected makes arrangements with Dr. Smith, a researcher in Minneapolis to send additional specimens. These arrive with a code that leaves Dr. Respected with no information about who the patients are. Many of the patients are still living. However, since outcome information may be required later, Dr. Smith retains a key to the patients' identities in his laboratory in Minneapolis. Some of the specimens were collected from other researchers in the Midwest and placed in Dr. Smith's bank in Minneapolis.

Q: Is Dr. Respected working with human participants?

A: Yes, because they are using tissue specimens from living individuals.

Q: Are these patients identified?

A: Yes, since the provider can relate the code to patient identity.

Q: Is the study exempt from the Common Rule (45 CFR 46)?

A: No, since the specimens can be identified.

Appendix B: Glossary

Adjuvant therapy:
One or more anticancer drugs used in combination with surgery or radiation therapy as part of the treatment of cancer. Adjuvant therapy is given before or after the primary treatment to increase the chances of a cure. Adjuvant usually means "in addition to" initial treatment.

Adverse event:
An unwanted and unintended occurrence affecting a human participant during research. Adverse events may be unexpected or expected.

Adverse event reports:
Researcher reports of all serious adverse events, injuries, and/or deaths given to the sponsor, the IRB, the FDA, and the NIH.

Assent:
Agreement by an individual not competent to give legally valid informed consent (e.g., a child or cognitively impaired person) to participate in research.

Assurance:
A written, binding commitment filed with a Federal agency by an institution that wishes to conduct human research. The institution promises to comply with applicable regulations governing human subject research and stipulates the procedures through which compliance will be achieved.

Autonomy:
Personal capacity to consider alternatives, make choices, and act without undue influence or interference of others.

Belmont Report:
The report entitled *Ethical Principles and Guidelines for the Protection of Human Participants of Research* generated by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1979. The ethical principles identified in this document: respect for persons, beneficence, and justice became the cornerstone of Federal regulation of protection for research participants.

Beneficence:
An ethical principle discussed in the Belmont Report that entails an obligation to protect persons from harm. The principle of beneficence can be expressed in two general rules: (1) do no harm; and (2) protect from harm by maximizing anticipated benefits and minimizing possible risks of harm.

Benefit:
A benefit in research is a valued or desired outcome enjoyed by the participant (therapeutic benefit), or accruing to a group under study, or to their family members, or to scientific knowledge (nontherapeutic benefit).

Certification:
The official notification by the institution to the supporting Department or Agency, in accordance with the requirements of 45CFR46, that a research project or activity involving human participants has been reviewed and approved by an Institutional Review Board in accordance with an approved assurance.

Child or children:
Persons who have not attained the legal age for consent to treatments or procedures involved in research under the applicable law of the jurisdiction in which the research will be conducted. Special rules and protections govern the participation of children in research.

Common Rule:
The "Common Rule" refers to Federal statutes governing the protection of human subjects in research, enacted in 1991 and adopted by 17 Federal agencies. The Common Rule is set forth in the Code of Federal Regulations, 45 CFR 46, and covers all federally funded research supported by the Departments of Agriculture, Energy, Commerce, HUD, Justice, Defense, Education, Veterans Affairs, Transportation, and HHS, as well as NSF, NASA, EPA, AID, Social Security Administration, CIA, and the Consumer Product Safety Commission. The provisions are identical to the DHHS Regulations (45 CFR 46, Subpart A).

Data:
Multiple facts (usually, but not necessarily, empirical) used as a basis for inference, testing, analysis, etc. or used as the basis for decision-making.

Data and Safety Monitoring Board (DSMB):
An independent committee that collects and analyzes data during the course of a clinical trial to monitor for adverse effects and other trends (such as an indication that one treatment is significantly better than another, that would warrant modification or termination of the trial, or notification of subjects about new information that might affect their willingness to continue in the trial. DSMBs are required by NIH for all Phase III clinical trials but may also be appropriate for Phase I and Phase II clinical trials if the studies have multiple clinical sites, are blinded (masked), or employ particularly high-risk interventions or vulnerable populations.

Data and Safety Monitoring Plan:
A plan with a general description of data and safety monitoring of a clinical research study. The plan is developed by the researcher, included in the protocol, and submitted to the IRB for review and approval before the study begins. An appropriate plan reflects the risks of the study, including its size and complexity.

Declaration of Helsinki:
Statement of ethical principles for human participation in biomedical research. The Declaration was first adopted in 1964 by the World Medical Association. The Declaration has been revised five times, most recently in 2000. Like the Nuremberg Code that preceded it, the Declaration of Helsinki makes consent a central requirement of ethical research. The Declaration initially established a distinction between the standards for therapeutic and nontherapeutic research; however, this has been eliminated in recent revisions.

Department or Agency head:
The head of any Federal Department or Agency and any other officer or employee of any Department or Agency to whom authority has been delegated.

Double Masked Design or "Double Blind" Design:
A study design in which neither the investigators nor the subjects know the treatment group assignments of individual subjects.

Embryo:
The developing organism from conception or implantation until approximately the eighth week of pregnancy.

Epidemiology:
A scientific discipline that studies the factors determining the causes, frequency, and distribution of diseases in a community or specified population.

Expedited Review:
Review of proposed research by the IRB Chair or a designated voting member or group of voting members rather than the entire IRB.

Exclusion Criteria:
The list of elements in a person's medical history that would prevent an individual from participating in a specific clinical trial.

Expected adverse event:
For approved and marketed drugs or devices, those adverse events described in the approved Package Insert (Label). For investigational new drugs or devices, those adverse events described in the FDA Investigator's Brochure. In clinical research studies, information on expected adverse events is summarized in the protocol and the consent form.

Fetus:
The product of conception from the end of the eighth week of pregnancy until birth or expulsion.

Food and Drug Administration (FDA):
An agency within the Department of Health and Human Services (DHHS) that monitors the manufacture, import, transport, storage, and sale of goods regulated under the Food, Drug and Cosmetics Act and related Federal public health laws.

Guardian:
An individual entitled or authorized to make decisions affecting the health or medical care of another, including the ability to consent.

Human participant (subject):
A living individual about whom an investigator conducting research obtains (1) data through intervention or interaction, or (2) identifiable private information.

Inclusion criteria:
The list of elements in a person's medical history necessary to allow an individual to participate in a specific clinical trial.

Informed consent:
A person's voluntary agreement, based upon adequate knowledge and understanding of relevant information, to participate in research. Informed consent also refers to the process of information exchange between researcher and participant prior to participation in research. The information to be conveyed to the participant is factual information, including an assessment of the risks of participation, eight specific elements required by Federal regulations, a description of the procedures that will be performed, and the persons responsible. The information conveyed by the participant to the researcher is an indication of his or her comprehension of the process, the voluntary nature of participation, and understanding of his or her rights, including the right to withdraw.
The informed consent form is a written document, signed by participants in research studies prior to commencement of the study. The form is presented to and signed by the participant, who should have a chance to ask questions regarding the research prior to the commencement of the study.

Institutional Review Board (IRB):
A specially constituted review body established to protect the welfare of human participants in research. Federal law states that all institutions supported by a Department or Agency to which the Common Rule applies must establish an IRB to review and approve research involving human subjects.

Institutional Review Board approval:
The determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and Federal requirements.

Intervention:
An action that produces an effect or that is intended to alter the course of a pathologic process. Includes both physical procedures by which data are gathered (e.g.,

venipuncture) and manipulations of the participant or the participant's environment performed for research purposes.

Institution:
Any public or private entity or Agency (including Federal, state, and other agencies); location of research.

Investigator:
In clinical trials, an individual who actually conducts an investigation [21 CFR 312.3]. Any interventions (e.g., drugs) involved in the study are administered to subjects under the immediate direction of the Investigator.

Justice:
An ethical principle discussed in the Belmont Report requiring fairness in the distribution of burdens and benefits; often expressed in terms of treating persons of similar circumstances or characteristics similarly.

Legally authorized representative:
An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective participant to his or her participation in the procedure(s) involved in the research.

Minor:
A person who has not attained the age of majority in a particular jurisdiction.

Minimal risk:
The probability and magnitude of harm or discomfort normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons**.**

National Institutes of Health (NIH)
The federal government's primary agency for advancing knowledge in biomedical and behavioral sciences in order to understand and treat human diseases. The NIH is part of the U.S. Public Health Service (PHS) within the Department of Health and Human Services.

National Research Act:
The law that authorized the creation of the National Commission for Protection of Human Subjects of Biomedical and Behavioral Research in 1974 and mandated review of research studies by institutional review boards.

Normal "Control" Volunteers:
Volunteer subjects used to study normal physiology and/or behavior or who do not have the condition under study in a particular protocol. Normal volunteers may be studied for comparison with subjects who have the condition under study.

Nuremberg Code:
A code of research ethics developed during the trials of Nazi war criminals following World War II. This code became the first international standard for the conduct of research and began the modern era of protection for human research participants.

Office for Human Research Protection (OHRP):
The office within the Department of Health and Human Services responsible for implementing DHHS regulations (45 CFR Part 46) governing research involving human subjects. The OHRP has oversight and educational responsibilities wherever DHHS funds are used to conduct or support research involving human participants

Office of Human Subjects Research (OHSR):
The office with the Department of Health and Human Services charged with interpreting and overseeing implementation of the regulations for the Protection of Human Subjects for research conducted at the Intramural Research Program (IRP) of the NIH.

Parent:
A person's biological or adoptive parent. In the conduct of research, the permission of the parent is generally necessary if the potential participant is a minor.

Permission:
The agreement of parent(s) or guardian(s) to the participation of their child or ward in research.

Phases of a Clinical Drug Trial:
Different stages of testing drugs in humans, from first application in humans (Phase I) through limited and broad clinical tests (Phase III), to post-marketing studies (Phase IV).

Phase I trial:
A clinical trial that serves as the initial introduction of an investigational new drug into humans. Phase I trials test physiologic factors, toxicity, and appropriate dosage. A Phase I trial often enrolls only a small number of patients.

Phase II trial:
Phase II trials include controlled clinical studies conducted to evaluate the drug's effectiveness for a particular indication in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug. These studies are typically well controlled, closely monitored, and conducted with a relatively small number of patients, usually involving no more than several hundred subjects.

Phase III trial:
Phase III trials involve the administration of a new drug to a larger number of patients in different clinical settings to determine its safety, efficacy, and appropriate dosage.

Phase III trials often enroll large numbers of people and may be conducted at many doctors' offices, clinics, and centers nationwide.

Pregnancy:
The state of a female after conception or implantation until the birth of a baby or expulsion of the fetus.

Principal Investigator:
The scientist or scholar with primary responsibility for the design and conduct of a research project, including preparation of the research protocol.

Prisoner:
An individual involuntarily confined or detained in a penal institution. This includes persons sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures that provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

Private information:
Information that is individually identifiable (i.e., the identity of the participant is or may readily be ascertained by the investigator) about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (e.g., a medical record).

Protocol:
Documentation of research objective, design, methods, statistical methods, and organization—includes amendments made to the original document. The research plan must include provisions for the adequate protection of the rights and welfare of prospective subjects and ensure that pertinent laws and regulations are observed.

Randomization:
Assignment of subjects to different treatments, interventions, or conditions according to chance rather than systematically (e.g., as dictated by the standard or usual response to their condition, history, or prognosis, or according to demographic characteristics). Random assignment of subjects to conditions is an essential element of experimental research because it makes more likely the probability that differences observed between subject groups are the result of the experimental intervention.

Recruitment:
The act of selecting and enrolling research participants for a study using proper inclusion criteria.

Research:
A systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Activities that meet this

definition constitute research for purposes of 45 CFR 46, even if they are conducted or supported under a program that is considered research for other purposes. For example, some demonstration and service programs may include research activities.

Researcher:
The individual who conducts and directs the study and carries the primary responsibility for the research. The Researcher is referred to as the Principal Investigator when acting as the leader of a research team.

Respect for Persons:
An ethical principle discussed in the Belmont Report requiring that individual autonomy be respected and that persons with diminished autonomy be protected.

Risks:
The probability of harm or injury (physical, psychological, social, or economic) occurring as a result of participation in a research study. Both the probability and magnitude of possible harm may vary from minimal to significant.

Risk/Benefit Analysis:
An analysis of the potential risks to participants considered against the potential benefits to the individual or to the research objectives of the study.

Sponsor:
An individual, company, institution, or organization that initiates and finances a research study. A sponsor is not necessarily the entity that conducts the research.

Therapy:
Treatment intended and expected to alleviate a disease or disorder.

Toxicity:
Having to do with poison or something harmful to the body. Toxic substances usually cause unwanted side effects to an organ system and/or to the participant's subjective status produced by therapy. Toxicities are graded numerically, with the lowest number representing no toxicity (e.g., 0 = none) and the highest number highest representing lethal toxicity (e.g., 5 = lethal).

Unexpected adverse event:
An adverse event not described in the Package Insert, Investigator's Brochure, published medical literature, protocol, or informed consent document.

Universal Declaration of Human Rights:
An international declaration adopted in 1948 by the United Nations as the first comprehensive agreement among nations as to the specific rights and freedoms of all human beings.

Voluntary:

Free of coercion, duress, or undue inducement. Used in the research context to refer to a subject's decision to participate (or to continue to participate) in a research activity.

Vulnerable participants/population:

Individuals or groups of subjects who, by reason of disability, illness, age, or other status exhibit diminished personal autonomy. Neither the Federal regulations nor ethical codes, including the Belmont Report, proscribe inclusion of vulnerable persons as research subjects. However, DHHS regulations mandate special justification for research involving fetuses, pregnant women, and human *in vitro* fertilization [45 CFR 46 Subpart B]; prisoners [45 CFR 46 Subpart C]; and children [45 CFR 46 Subpart D].

Appendix C: Resources

- Guidance Topics by Subject
  http://ohrp.osophs.dhhs.gov/g-topics.htm

- Infosheets, Forms, Checklists.
  http://ohsr.od.nih.gov/info

- Office for Human Research Protections
  http://ohrp.osophs.dhhs.gov/

- U.S. Food and Drug Administration
  http://www.fda.gov/

- National Bioethics Advisory Commission
  http://bioethics.gov/

- Interpretive Guide to the Federal Policy for the Protection of Human Subjects
  http://www.usaid.gov/pop_health/resource/phncomrule.htm

- Office of Human Subjects Research
  http://ohsr.od.nih.gov/

- Office of Extramural Research
  http://grants.nih.gov/grants/oer.htm

- Bioethics Resources on the Web
  http://www.nih.gov/sigs/bioethics

- Ethical Issues in Research Involving Human Participants - Current Bibliographies in medicine 99-3
  http://www.nlm.nih.gov/pubs/cbm/hum_exp.html

- Information about cancer research studies
  http://cancertrials.nci.nih.gov/

Appendix D: Table 1

Information to be Included in the Consent Document (adapted from 45CFR.46.116)

1. A statement that the study involves research.

2. An explanation of the purpose of the research, an invitation to participate and explanation of why the participant was selected, and the expected duration of the participant's participation.

3. A description of procedures to be followed and identification of which procedures are investigational and which might be provided as standard care to the participant in another setting. Use of research methods such as randomization and placebo controls should be explained.

4. A description of any foreseeable risks or discomforts to the participant, an estimate of their likelihood, and a description of what steps will be taken to prevent or minimize them; as well as acknowledgment of potentially unforeseeable risks.

5. A description of any benefits to the participant or to others that may reasonably be expected from the research, and an estimate of their likelihood.

6. A disclosure of any appropriate alternative procedures or courses of treatment that might be advantageous to the participant.

7. A statement describing to what extent records will be kept confidential, including examples of who may have access to research records such as hospital personnel, the FDA, and drug sponsors.

8. For research involving more than minimal risk, an explanation and description of any compensation and any medical treatments that are available if participants are injured through participation; where further information can be obtained, and whom to contact in the event of research-related injury.

9. An explanation of whom to contact for answers to questions about the research and the research participant's rights (including the name and phone number of the Principal Investigator (PI)).

10. A statement that research is voluntary and that refusal to participate or a decision to withdraw at any time will involve no penalty or loss of benefits to which the participant is otherwise entitled.

11. A statement indicating that the participant is making a decision whether or not to participate, and that his/her signature indicates that he/she has decided to participate having read and discussed the information presented.

Appendix E: Faculty

This program was developed by The National Cancer Institute in collaboration with The National Institute of Allergy and Infectious Diseases, The National Heart, Lung and Blood Institute, The National Institute of Neurological Disorders and Stroke and The National Institute of Mental Health.

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